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OBSERVATIONS ON THE OCCURRENCE OF INVERTED AND DIPHASIC P-WAVES IN LEAD III OF THE HUMAN ELECTROCARDIOGRAM*

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AND

ALFRED M. WEDD, M.D.

PITTSBURGH

Apart from the inversion of the P-wave met with in Lead III in the human electrocardiogram in the presence of an ectopic, heterogenous rhythm,¹ associated with a definite change in the location of the pacemaker, and as a result of disturbances in the respiratory rhythm, such negativity of the atrial deflection is but occasionally seen, though it has seemed to us that the frequency of its incidence in this derivation in pathologic hearts is greater than one is led to expect from a review of the literature.

That Lead III shows the greatest susceptibility to these changes of form and direction is a fact of common observation, and the frequent inversion of the T-wave seen in this lead in otherwise normal galvanometric curves is additional evidence of the variation in electrical negativity met with in clinical observations.

It has been shown by Einthoven, Fahr and de Waart² that the P-deflection in the third lead of the electrocardiogram may be conspicuously modified by the phases of respiration, being lower at the end of inspiration and beginning expiration, coinciding in this respect with the longer pauses of the cardiac cycle. They state that following a long pause in this lead (L_3) "P may appear of lower voltage (klein), at times diphasic, and again wholly negative, while following the short pauses, that is with greater cardiac frequency and diminished vagus tone, P again assumes its normal form and size." They further caution against the difficulties encountered in attributing these changes purely to the influence of respiration, because of the effect of the change in the position of the heart that comes into play. Assuming

* Submitted for publication Aug. 13, 1918.

* From the Medical Clinic of the Cleveland City Hospital* and the Western Reserve University.

1. Lewis, T.: Quart. J. Med., 6:221, 1913; Idem., Heart, 2:23, 1910.

2. Einthoven, W., Fahr, G., and de Waart, A.: Pflüger's Arch. f. d. ges. Physiol., 150:175, 1913.

as an added factor in the explanation of this change in the P-wave "that a slight rotation of the heart about the sagittal axis of the body, as is possible with a deep inspiration, is sufficient to modify conspicuously the form and height of the various complexes."

As bearing on the negativity of P in Lead III, the suggestions of Hering³ in reference to the curves seen in *situs transversus* are of interest, only in so far, however, as they may apply to the inversion of P in this lead (L_2). This observer advances the theory that the inverted P in true congenital dextrocardia may be due to the fact that the excitation wave in the transposed heart arises from a focus lying nearer that lead from which under normal conditions it is furthest away. Thus explaining the reversal of negativity on the purely physical basis of the relationship of the heart to the sagittal axis in a given lead. It should be recalled that in *situs transversus* this inversion of negativity affects Lead I alone. In this connection the interesting papers by Samojlhof⁴ may be referred to.

In their experimental work on the dog's heart, Lewis, Meakins and White⁵ have demonstrated a migration of the pacemaker within the S-A node following vagal stimulation, associated with a shortening of the conduction time between the leads employed and characterized by negative galvanometric curves. Further observations on alterations in the P-deflections following experimental vagus stimulation have been described by Einthoven⁶ and by Meek and Eyster,⁷ who have also studied the effect of such stimulation on the location of the pacemaker.

In reporting three cases characterized by an inversion of the P-wave associated with respiration, Wilson⁸ has ascribed the negativity of P as due to a change in the location of the pacemaker, and has divided these changes into three classes: migration within the sinus node, or its immediate neighborhood, migration from the S-A node to the A-V node, and, third, escape of the idioventricular rhythm.

In alluding to similar inverted P-waves seen in Lead III, Wilson and Robinson⁹ advance the view that this inversion is analagous to the changes that may occur in the experimental animal under vagal stimulation.

3. Hering, H. E.: Prag. med. Wchnschr., **10**:133, 1911; cited by Kahn (Footnote 14).

4. Samojlhof, A.: Pfluger's Arch. f. d. ges. Physiol., **153**:196, 1913; Idem., Zentralbl. f. Herz u. Gefasskrankh., **6**:201, 1914.

5. Lewis, T., Meakins, J., and White, P. D.: Phil. Tr. Roy. Soc. London, 1914, Series B., pp. 205, 375.

6. Einthoven, W.: Arch. f. d. ges. Physiol., **122**:517, 1908.

7. Meek, W. J., and Eyster, J. A. E.: Heart, **5**:227, 1914.

8. Wilson, F. N.: ARCHIVES INT. MED., **16**:989, 1915.

9. Wilson, F. N., and Robinson, G. C.: ARCHIVES INT. MED., **21**:166, 1918.

10. Goddard, C. H.: ARCHIVES INT. MED., **16**:631, 1915.

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In a paper on the changes in the P-wave in the human electrocardiogram, Goddard¹⁰ has noted the greater frequency of these seen in Lead III, P₁ being inverted in but four, P₂ in but seven and P₃ in seventy-five of the total of his series of 700 cases. Whether or not the inversion of P in Leads I, II and III was associated with any change in conduction time is not stated, and as there is no statement as to the effect of atropin or digitalis on these inverted P-waves, it is difficult to classify them.

Following right vagal stimulation, conspicuous alteration in the form of the P-wave seen in Lead II has been noted by Ritchie.¹¹

In his fundamental paper on the effect of digitalis on the human electrocardiogram Cohn¹² has shown that the inversion of T seen under the effect of digitalis may be influenced by atropin; that when, after a course of digitalis, the T-wave fails to show the usual reversal, this may be masked by the inhibitory effect of the vagi, and then after atropin T becomes more negative or inverted. The altered T-wave which atropin fails to affect he attributes to the action of the digitalis on the cardiac muscle. Cohn does not describe any change in the P-wave in Lead III, following digitalis, such as we have observed.

DETAILED REPORT OF ELECTROCARDIOGRAMS

In abstracting the case reports of the individuals on whom this study is based we have omitted as irrelevant all details as to the history and clinical course, giving only the clinical diagnosis, together with such notes as are essential in the interpretation of the figures.

CASE 1.—J. G., aged 72. Clinical diagnosis: complete atrioventricular dissociation with Stokes-Adams syndrome, known to be of two years' duration. The patient was admitted to the hospital again in November, 1917.

Electrocardiograms: Records taken in May, 1916, showed no abnormalities in the P-wave. In the records taken the day after admission, Nov. 5, 1917, all P-waves are upright¹³ in the three leads.

After taking 4 c.c. of tincture of digitalis daily for ten weeks with absolutely no symptoms of disturbance, P₂ is diphasic or inverted, but becomes upright immediately after the administration of 2 mg. of atropin (Fig. 1, A, and B).

Records taken two months after digitalis had been discontinued show P₂ regularly upright.

Summary: Inverted and diphasic P₂ following the administration of digitalis, rendered upright by atropin.

CASE 2.—W. S., aged 62, No. 279. Clinical diagnosis: chronic myocarditis with intraventricular block.

Electrocardiograms: In the records taken before the administration of digitalis the P-wave was upright in all three leads. Records taken after 77.5 c.c. of tincture of digitalis had been given showed an inverted or a

11. Ritchie, W. T.: *Quart. J. Med.*, 6:47, 1912.

12. Cohn, A. E.: *J. Exper. Med.*, 21:593, 1915.

13. We use the words "upright" and "inverted" as synonymous with positive and negative, a positive wave representing primary base negativity, and a negative wave primary apex negativity.

diphasic P_s . But in the records taken the next day, twenty-four hours later, after 87.5 c.c. of digitalis, P_s was regularly upright. Atropin was not given at the time of the inversion (Fig. 2, A and B).

Summary: Transient inverted and diphasic P_s occurring during the administration of digitalis. P-R interval 0.16 sec. with both upright and inverted P_s .

CASE 3.—J. K., aged 59, No. 345. Clinical diagnosis: chronic myocarditis, probably luetic in origin.

Electrocardiograms: Normal mechanism; left ventricular preponderance; S_2 notched. T_1 small and upright; T_2 and T_3 inverted. P_s inverted or diphasic. P-R interval in Leads I and II, 0.16 sec. P-R interval in Lead III, with invert P , 0.12 sec.



Fig. 1.—Case 1. Lead III. Complete a-v dissociation. A, P_s inverted following digitalis. B, after atropin P_s upright. In this as in all the figures, one division of ordinates equals 0.04 sec.

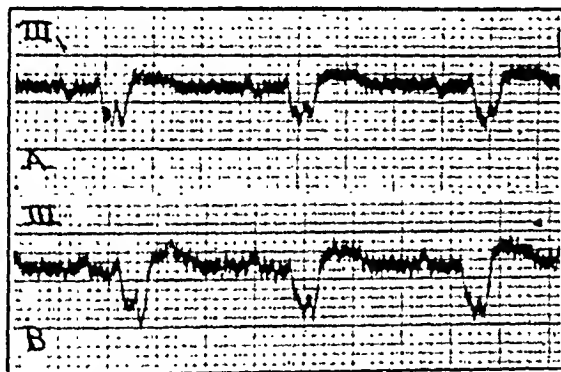


Fig. 2.—Case 2. Lead III. A, after 77.5 c.c. of digitalis P_s inverted or diphasic. P-R interval 0.16 sec. with both upright and inverted P_s . B, twenty-four hours later, after 87.5 c.c. of digitalis P_s upright.

P_s was probably rendered upright by 2 mg. of atropin, though the curves are ragged (Fig. 3, A and B).

After 14 c.c. of tincture of digitalis, P_s was definitely upright and remained so during the administration of digitalis (Fig. 3, C).

Record taken at the time of discharge, eight days after the last digitalis had been given, showed a variable P_s , upright, diphasic or inverted (Fig. 3, D).

Summary: Inverted or diphasic P_s , rendered upright by atropin, becoming inverted again after recovery from the atropin, then rendered upright by the administration of digitalis and remaining upright throughout its administration, becoming again variable eight days after the last digitalis had been given, when it appears upright, diphasic or inverted.

CASE 4

CASE 4.—M. J., aged 5
cardiac hypertrophy, 227

Electrocardiogram:
 T_1 and T_2 inverted. P_s
seen in all three leads.

P_s is not altered by
Summary: Permanent
by digitalis and atropin.

CASE 5.—W. T., aged
carditis with myocardial
Electrocardiogram:
diph. ventricular fibrillation
in all three leads.

Fig. 3.—Case 3.
P-R interval 0.12 sec.
C after 14 c.c. of d
P variable, upright.

After 15 c.c. of d
normal measures 0.1
Fifteen minutes a
in P-R interval 0.12

Summary: A case
by digitalis, and d
inversion was intere

CASE 6.—J. B., 22
with transient right

CASE 4.—M. J., aged 55, No. 364. Clinical diagnosis: chronic myocarditis, cardiac hypertrophy, arteriosclerosis.

Electrocardiograms: Normal mechanism; left ventricular preponderance. T_1 and T_2 inverted. T_3 upright. P_2 diphasic or inverted. P-R interval 0.25 sec. in all three leads.

P_2 is not altered by digitalis or by atropin (Fig. 4).

Summary: Permanent inverted or diphasic P_2 not induced by or affected by digitalis and not affected by atropin.

CASE 5.—W. T., aged 44, No. 342. Clinical diagnosis: chronic mitral endocarditis with myocardial failure. Died. No necropsy permitted.

Electrocardiograms: Normal mechanism. Occasional premature contractions, ventricular in origin. Left ventricular preponderance. P-waves upright in all three leads. P-R interval 0.22 sec. (Fig. 5, A).

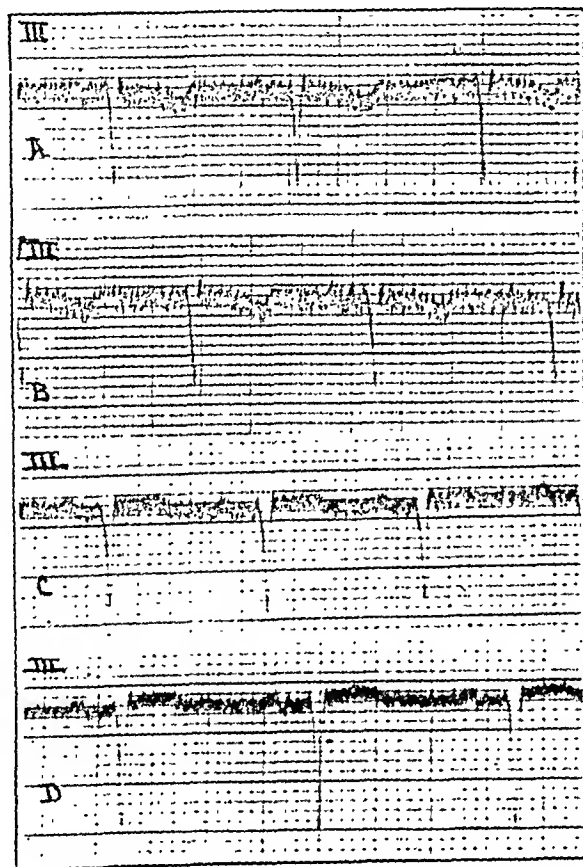


Fig. 3.—Case 3. Lead III. A, before digitalis, P_2 inverted and diphasic. P-R interval 0.12 sec. B, after atropin, P_2 probably upright, curves ragged. C, after 14 c.c. of digitalis, P_2 upright. D, eight days after last digitalis, P_2 variable, upright, inverted and diphasic.

After 18 c.c. of tincture of digitalis, P_2 was definitely inverted. The P-R interval measures 0.17 sec. (Fig. 5, B).

Fifteen minutes after 2 mg. of atropin P_2 became upright and remained so. P-R interval 0.18 sec. (Fig. 5, C).

Summary: A case in which the P-wave in Lead III was definitely inverted by digitalis, associated with a shortening of the conduction time, and this inversion was overcome by atropin.

CASE 6.—J. B., aged 46, No. 355. Clinical diagnosis: chronic myocarditis with transient right bundle-branch lesion.

CASE 7.—O. B., aged 45, No. 351. Clinical diagnosis: cardiorenal disease with myocardial failure; tabes dorsalis.

Electrocardiograms: Very low voltage; notched R and S, conspicuous in Lead II. All T- and P-waves upright. P-R interval measures 0.14 sec. in all three leads (Fig. 7, A).

After 96 c.c. of tincture of digitalis had been given, with absolutely no symptoms referable to the drug, there was a complete A-V dissociation with an irregular inversion of P_a (Fig. 7, B).

Thirty minutes after 2 mg. of atropin the mechanism was normal with a diphasic P_a . The P-R interval averaged 0.17 in Leads II and III. Twelve hours later P_a was definitely upright (Fig. 7, C).

Summary: The production of a complete dissociation by digitalis with an inversion of P_a . Restoration of the normal mechanism and reversion of P_a promptly induced by atropin.

CASE 8.—T. L., aged 16, No. 266. Clinical diagnosis: chronic mitral endocarditis, chronic pericarditis, rheumatic in origin.

Electrocardiograms: Normal mechanism. Occasional premature atrial systoles associated with an inverted P in all three leads. P_a , however, is con-

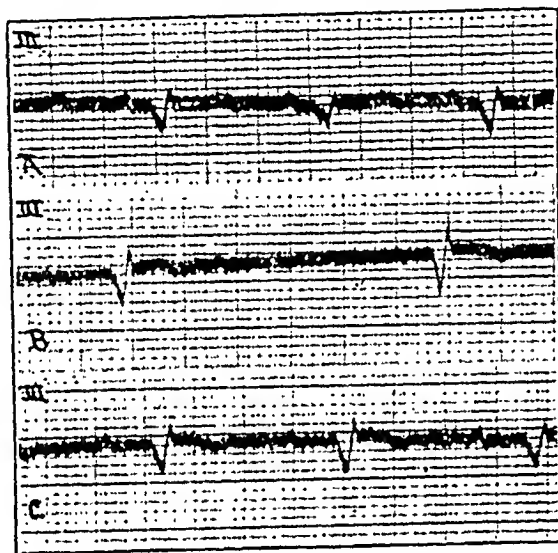


Fig. 7.—Case 7. Lead III. B, after 96 c.c. of digitalis, complete a-v dissociation with irregular inversion of P_a . C, after atropin, normal mechanism with diphasic P_a .

stantly inverted, remaining so in the absence of, as well as in the presence of, the extrasystoles. The P-R interval in Leads I and II during the normal mechanism measures 0.14 sec. With the occurrence of the extrasystole it is shortened, measuring 0.12 sec. In Lead III the P-R interval measures constantly 0.12 sec., being the same in the presence of the extrasystole and during the normal mechanism. In Fig. 8, A and B, we give both Lead II and III to show this dissimilarity (Fig. 8, A and B).

The administration of 12 c.c. of tincture of digitalis produced marked physiologic effect, with a coupled rhythm, but had no effect on the inverted P_a . The administration of 2 mg. of atropin had no effect on the inverted P_a . Vagus pressure was also without effect.

Records taken twenty days after the discontinuance of the digitalis showed P_a inverted as before (Fig. 8, C).

Summary: This patient was under observation for over a year, having been admitted to the hospital, in all, four times in the previous fourteen months. On all previous admissions P_a was always inverted. This case illustrates the

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presence of a persistent inverted P_3 occurring in a pathologic myocardium, not related to digitalis action and also unaffected by atropin or by vagus pressure. In records taken two months later the extrasystoles were absent. P_3 was still inverted.

CASE 9.—A. K., aged 25, No. 330. Clinical diagnosis: chronic endocarditis of the mitral valve and extreme decompensation; mitral stenosis.

Electrocardiograms: Normal mechanism. Right ventricular preponderance. P-waves upright in all three leads; broad and bifurcated in Leads I and II, typical of the form seen in mitral stenosis.

After the administration of 85 c.c. of tincture of digitalis, T_1 remained upright, T_2 and T_3 were inverted. The P-R interval measured 0.22 sec. (Fig. 9, A).

Seven days after the foregoing record was taken and ten days after the digitalis had been discontinued the broad and notched P-waves in Leads I

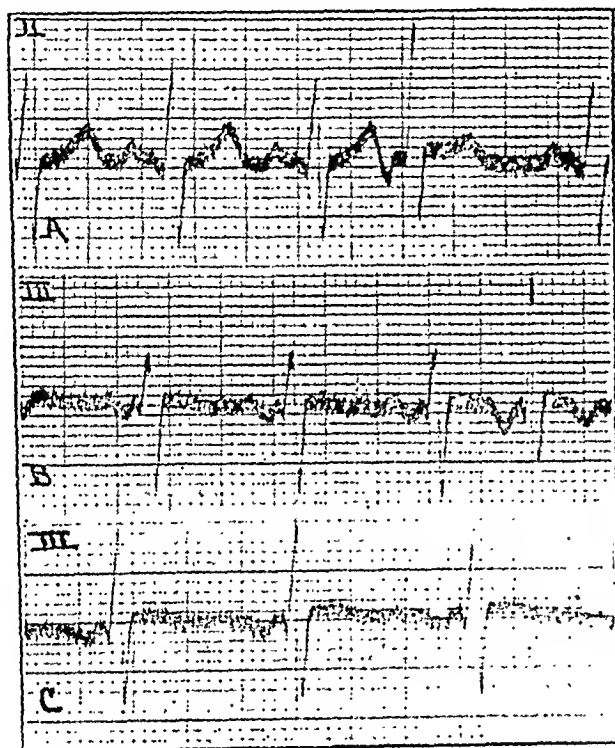


Fig. 8.—Case 8. Leads II and III. P-R interval 0.12 sec in all three leads. P_3 permanently inverted. A, to show extrasystole in Leads II and III. C, twenty days after last digitalis.

and II had disappeared and P_3 was definitely inverted. The P-R interval in Leads I and II measured 0.17 sec. In Lead III with the invert P, 0.11 sec. (Fig. 9, B).

Summary: A case showing a variation in the P-waves, with inversion of P_3 ten days after the discontinuance of digitalis. The relation of the invert P_3 to digitalis or to vagus effect is not definitely known, but on admission six weeks later P_3 was found to be diphasic or inverted, and we believe this to be an instance in which an inverted P_3 was rendered upright by digitalis.

CASE 10.—J. P., aged 40, No. 327. Clinical diagnosis: chronic myocarditis and chronic valvular disease, luetic and rheumatic in origin; confirmed by necropsy.

Electrocardiograms: Normal mechanism. Occasional premature systoles of ventricular origin. Left ventricular preponderance. The P-R interval measured 0.14 sec. in all three leads. P_3 is inverted or diphasic.

After 80 c.c. of tincture of digitalis had been given P_2 was definitely inverted. This inversion was not influenced by vagus pressure, by deep breathing, or by the administration of 2 mg. of atropin. There was no sinus escape after atropin though there was a slight shortening of the P-R interval by 0.03 sec. This observation was repeated and confirmed three days after stopping the digitalis (Fig. 10).

The last records taken seventeen days after digitalis had been discontinued showed P_2 still inverted.

Summary: This case is believed to illustrate an inverted P-wave in Lead III, occurring in a pathologic myocardium, which is not subject to vagus control and is not influenced by digitalis or by atropin.

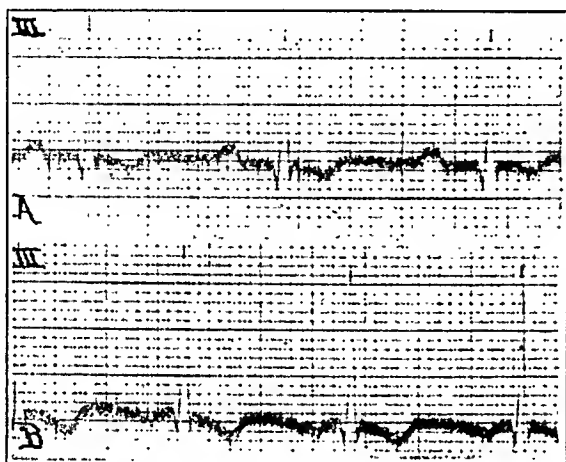


Fig. 9.—Case 9. Lead III. A, after 85 c.c. of digitalis, P_2 upright. Note the broad P-wave. P-R interval 0.22 sec. B, seven days after "B," and ten days after last digitalis, P_2 inverted. P-R interval 0.11 sec. Note the sharp negative P-wave.

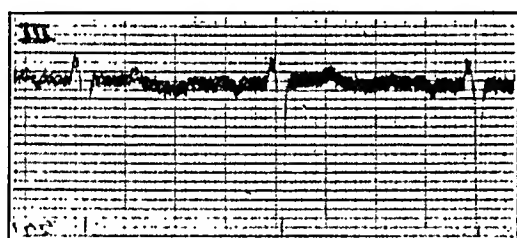


Fig. 10.—Case 10. Lead III. P-R interval 0.14 sec. in all three leads. P_2 permanently inverted.

CASE 11.—P. B., aged 34, No. 334. Clinical diagnosis: chronic myocarditis, mitral insufficiency with a moderate grade of decompensation.

Electrocardiograms: Normal mechanism. P_2 definitely inverted. The P-R interval measures 0.17 in Leads I and II. In Lead III with inverted P the P-Q interval measures 0.08 sec. This record was taken after 8 c.c. of digitalis had been given (Fig. 11, A).

After 62 c.c. of tincture of digitalis had been given P_2 was definitely upright. The P-R interval in Leads I and II then measured 0.18. In Lead III the P-Q interval measures 0.17 sec. (Fig. 11, B).

Digitalis was continued until 98 c.c. of the tincture had been given. A marked sinus arrhythmia developed. P_2 remained upright. Six days after

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discontinuing the digitalis P_2 is diphasic or upright (Fig. 11, C). Twenty-four hours later, P_2 was inverted. Following the administration of 2 mg. of atropin it became upright in twenty minutes (Fig. 11, D and E).

Two weeks after the last digitalis had been given the P-wave in Lead III showed a spontaneous change from an inverted to an upright P_2 (Fig. 12, F).

Later on P_2 though still inverted became upright during pressure on the right vagus (Fig. 12, G).

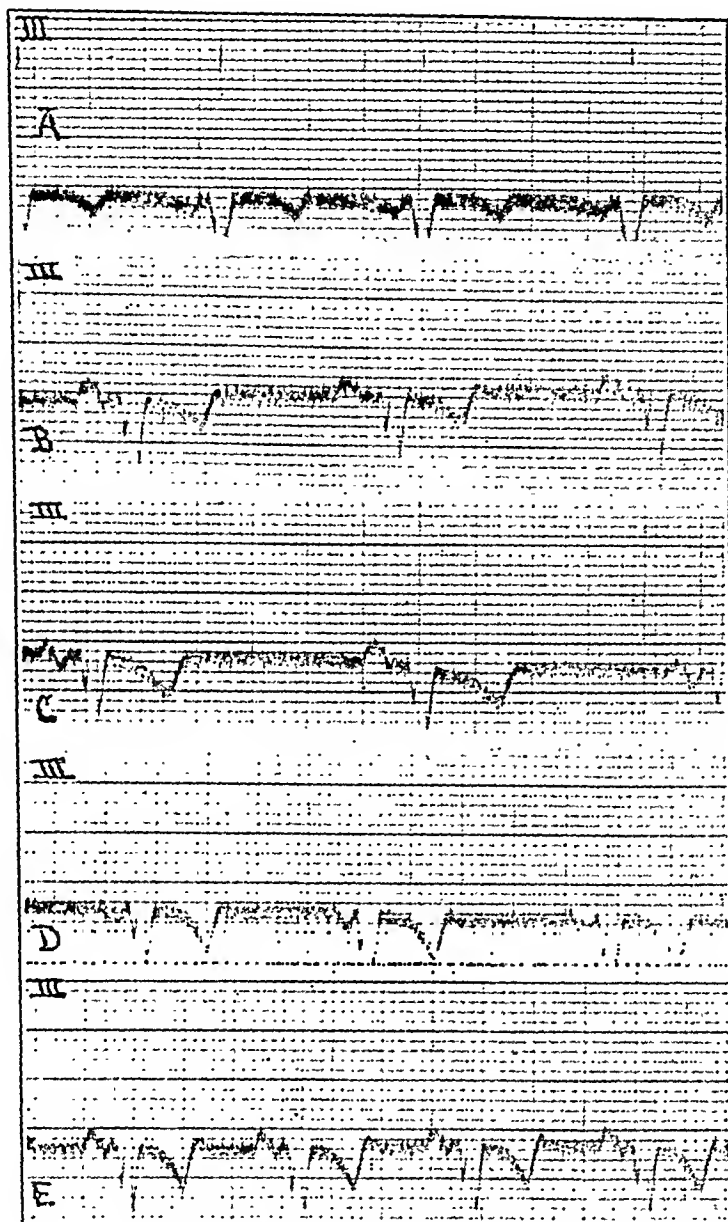


Fig. 11.—Case 11. Lead III. A, after 8 c.c. of digitalis. P-R interval 0.08 sec. P_2 inverted. B, after 62 c.c. of digitalis, P_2 upright. P-R interval 0.17 sec. C, after 98 c.c. of digitalis, P_2 still diphasic or upright. D, seven days after the last digitalis (twenty-four hours later than "C"), P_2 inverted again. E, after atropin, P_2 upright.

During deep breathing marked variations occurred. P_2 appearing upright, inverted or diphasic (Fig. 12, H).

Summary: A case illustrating an inverted P_2 with reversion of its negativity following digitalis, atropin, vagus stimulation and deep breathing, and showing also a spontaneous variation in the negativity of P in Lead III.

CASE 12.—T. G., aged 45, No. 361. Clinical diagnosis: chronic myocarditis, chronic valvular disease and aortitis.

Electrocardiograms: Normal mechanism. Left ventricular preponderance. T₁ upright, T₂ and T₃ inverted. P₂ inverted and diphasic. The P-R interval measures 0.18 sec. in all three leads (Fig. 13, A).

Twenty minutes after the administration of 2 mg. of atropin P₂ became upright. The wave was then quite broad, and the P-R interval was shortened

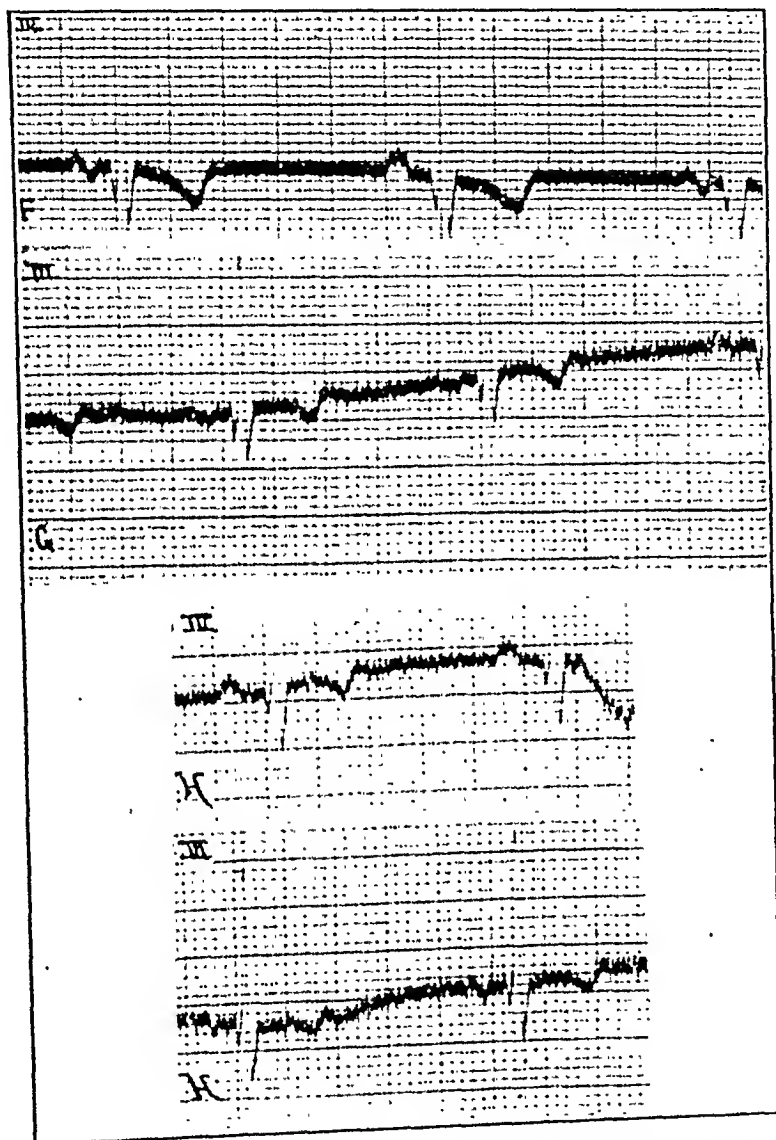


Fig. 12.—Case 11. Lead III, F. Two weeks after digitalis had been discontinued, spontaneous variation in P₂. G, later, P₂ rendered upright by pressure on the right vagus. H, P₂ shows marked variations on deep breathing, upright, inverted and diphasic. P-R interval 0.18, 0.14 and 0.12 sec. This figure cut from a continuous record.

to 0.16 sec. Digitalis was started and the P-wave continued upright during the period of observation (Fig. 13, B).

Summary: A case in which, in the records taken on admission, P₂ was inverted, was promptly rendered upright by 2 mg. of atropin and remained upright during the period of observation throughout which he was taking digitalis.

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The foregoing cases may be tabulated as in Table 1.

TABLE 1.—TABULATION OF ELECTROCARDIOGRAMS

Findings	Cases
Positive P_3 inverted by digitalis.....	1, 2, 5 and 7
Negative P_3 rendered upright by digitalis.....	3, 6, 9, 11 and 12
Negative P_3 rendered upright by atropin.....	1, 3, 5, 6, 7, 11 and 12
Negative P_3 persistent, not affected by digitalis, atropin or vagus pressure.....	4, 8 and 10
P-R interval the same with positive and negative P_3 (after digitalis).....	2, 4, 6, 10 and 12
P-R interval with negative P_3 shorter (after digitalis).....	3, 5, 8, 9 and 11
Negative P_3 with both normal and ectopic rhythm.....	8

DISCUSSION OF CASES

By reference to Table 1 it will be seen that in four cases (1, 2, 5, and 7) a normally positive P-wave in Lead III was rendered negative following digitalis. This digitalis effect is marked in Cases 5 and 7 (see corresponding figures). It is also seen that in the presence of a negative P-wave in Lead III this was rendered positive by digitalis in four instances (Cases 3, 6, 11 and 12). See the corresponding figures.

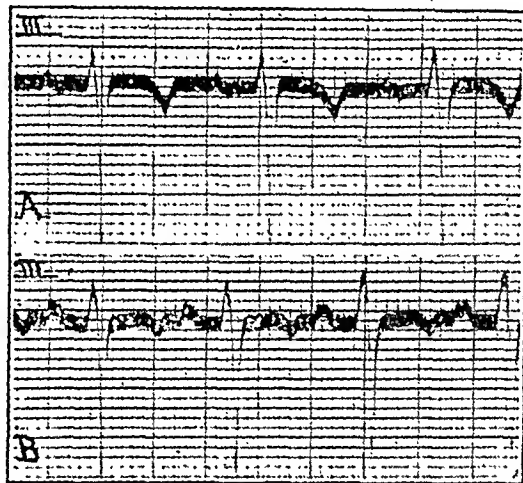


Fig. 13.—Case 12. Lead III. P-R interval 0.18 sec. in all three leads. A, before digitalis P_3 inverted or diphasic. B, after atropin P_3 upright and broad. P-R interval 0.16 sec.

In seven instances with a negative P_3 , 2 mg. of atropin promptly reversed this negativity, rendering the P-wave upright.

In three instances the inverted P-wave in Lead III was permanent, being absolutely uninfluenced by digitalis, atropin or vagus pressure (Cases 4, 8 and 10).

The P-R Interval.—Of the eight cases of our series with an originally negative P-wave in Lead III, in four (4, 6, 10 and 12) the P-R interval measured the same in all three leads, and in four (3, 8, 9 and 11) is shorter in the third lead with the negative P_3 . In Case 4, of the first group, there was a definite pathologic increase in the conduction time in all leads.

Relationship of the Inverted P₃ to the T-Wave in the Same Lead.—

It is obviously difficult to tabulate the relationship of the inverted P-wave in Lead III to the T-wave in the same lead, inasmuch as digitalis was given in every case, and in several instances the P-wave showed a great variability in its negativity, notably Case 8. In the records taken on admission or at the time the inversion of P₃ was first noted, this relationship was as shown in Table 2.

TABLE 2.—RELATIONSHIP OF INVERTED P₃ TO T-WAVE

P ₃	T ₃	Cases
Negative	Positive	1, 4, 5, 6, 10
Negative	Negative	2, 3, 7, 8, 9, 11, 12*

* P₃ in Case 12, Figure 12, was more often diphasic.

Thus it will be seen from Table 2 that the constancy of the relationship is about equally divided between the presence of a negative P₃ and T₃ and a negative P₃ with a positive T₃.

The Inversion of P₃.—In four of the cases cited the inversion of the P-wave in Lead III was definitely due to the effect of digitalis, and we believe that this inversion is brought about by a change in the muscle balance affecting the electrical negativity in this lead analogous to the alterations causing an inversion of T, and we attribute the corresponding reversal, also seen in four instances, in the presence of a negative P₃ to the same action. That this negativity of the P-wave is also under the influence of the vagi is evident from the reversal that occurred following atropin; though this reversal does not correspond with the effect of atropin on the T-wave made negative by digitalis (Cohn¹²). We consider that this difference may be due to the influence of the digitalis on the volume of atrial muscle mass involved.

In addition to the four instances of a negative P₃ following digitalis there remain seven cases in which a negative P₃ became positive following atropin (Cases 1, 3, 5, 6, 7, 11 and 12). One of these, in which P₃ was first negative, became positive under digitalis and then reverted again, becoming negative seven days after the digitalis had been discontinued; there was a reversal of the invert P both after atropin (Fig. 11, *d* and *e*) and following pressure on the right vagus (Fig. 11, *g*), a paradoxical reaction the essential nature of which is not clear. It is true that this case showed a remarkable spontaneous variation in the negativity of P₃ that was also influenced by deep breathing. We believe that this case illustrates a definite change in the location of the pacemaker in this lead, attributable to vagus influence, with which the greatly shortened conduction time in the presence of the inverted P₃ is consistent.

Of greater interest are the three cases (4, 8 and 10) which showed a persistent negative P-wave in Lead III uninfluenced by digitalis,

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atropin, vagal pressure or deep breathing. One of these (8) had a markedly shortened conduction time, 0.12 sec., one (10) a shorter conduction time after atropin, 0.11 sec., and one (4), with a pathologic increase in the P-R interval, a conduction time the same in all three leads, 0.25 sec.

Of these, Case 8 is perhaps the most instructive, as it offers an opportunity to compare the normal rhythm in all three leads with that in the presence of atrial extra systoles, the negative P-wave in Lead III persisting during the normal mechanism and in the presence of the ectopic stimulus (Fig. 8, *a*). With the extra systole the conduction time measures the same in all three leads, 0.12 sec., and in Lead III it remains constant at this figure during the normal rhythm and with the extra systole.

In Lead II we are dealing with an ectopic focus as the origin of the extra systole. In Lead III, considering the extra systole alone, the same conclusion is justifiable, but what shall be said for the inverted P_3 present constantly in this lead in the absence of the extra systole? We believe that the inverted P_3 represents a change of location for the pacemaker in this lead which, in response to the early ectopic impulse, gives rise to an exaggerated negativity (Fig. 8, *a*).

Assuming a demonstrable shortening of the conduction time, together with an inverted P_3 , as evidence in favor of the view that there is a definite change in the location of the pacemaker in Lead III, four cases would fulfill this requirement (3, 8, 9 and 11), though two cases of our series (4 and 10) had permanently negative P-waves in Lead III, one of these, however, (4) associated with a definite pathologic increase in conduction time in all leads.

In his paper, previously referred to, Wilson⁹ has recorded the abrupt onset, during deep breathing, of an ectopic rhythm originating in the A-V node associated with a definite sudden shortening of the P-R interval seen in Lead II. At no time have we been fortunate enough to catch any change in the location of the pacemaker, attributable to vagal influences or digitalis other than in Lead III.

The Diphasic P-Waves.—The presence of a P-wave essentially diphasic, such as is so well illustrated by Figure 13, and is also so often seen following vagal stimulation, deep breathing, or during digitalis administration, can only mean that there is a great variability in the electrical negativity of the excitation wave in the atrial wall in Lead III, dependent on digitalis effect or vagal tone and influenced possibly by the peculiar relationship of this derivation to the course of the excitation wave in the atrial wall.

It is, of course, possible that these diphasic curves though seen only in one lead (III) may represent an interference with the normal course of the excitation wave for this derivation and in this sense may

be looked on as evidence of pathologic change. There is some evidence in favor of this view in the alteration sometimes seen under digitalis in the typical notched or broadened P-waves present in all leads in some instances of mitral stenosis (Fig. 9 *a* and *b*). For a discussion of the literature up to 1914, see Kahn's¹⁴ monograph.

We believe that we may divide our series of inverted P-waves, seen in Lead III, into two distinct groups; one in which there may be a variation in the site of the pacemaker in its relation to Lead III, conspicuously under the influence of the vagi and digitalis, and a second group in which the relationship of the pacemaker to Lead III is such that a constantly negative P_3 is present utterly uninfluenced by atropin, vagal pressure or digitalis, due possibly to a change of the muscle balance altering the relation of the pacemaker to the axis for this derivation, or to the anatomic distribution of the vagal fibers.

Group I may be looked on as falling into the first and second class described by Wilson as migration of the pacemaker within the s-a node, its immediate neighborhood, or to the a-v node, while Group II, on theoretical grounds, may be considered as a distinct group, though there are difficulties in the way of a too arbitrary division.

CONCLUSIONS

1. The administration of digitalis may lead to an alteration in the negativity of the P-wave in Lead III of the human electrocardiogram.
2. Three instances of the presence of a persistently inverted P-wave, in Lead III, uninfluenced by vagus pressure, atropin, digitalis or deep breathing are recorded.
3. Excepting in the presence of a permanently negative P_3 , the electrical negativity of the inverted P-waves in Lead III is reversed by atropin.
4. Additional evidence is cited showing the effect of the vagi on a change in the location of the pacemaker in Lead III.

14. Kahn, R. H.: *Ergebn. d. Physiol.*, 14:1, 1914.

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EPIDEMIC CEREBROSPINAL MENINGITIS AS
OBSERVED AT GENERAL HOSPITAL
NO. 6, FORT McPHERSON, GA.,
WINTER OF 1917 AND 1918*

C. N. B. CAMAC, M.D.
Lieutenant-Colonel, M. C., U. S. A., Chief Medical Service

AND

KARL M. BOWMAN, M.D.
Captain, M. C., U. S. A., Ward Surgeon

FORT MCPHERSON, GA.

This report includes cases of epidemic cerebrospinal meningitis at General Hospital No. 6, Fort McPherson, Georgia, from Oct. 1, 1917, to May 1, 1918, a period of seven months. Ten patients were treated and the diagnosis was confirmed in every case by the presence of the meningococcus in the spinal fluid.

Methods Employed in Care of Meningitis Cases.—Meningitis patients were isolated in single rooms. Clothing, bed clothes, dishes, bedpans and urinals were sterilized. Throat cultures were taken from convalescent patients every four days until three negative cultures were obtained, and from physicians, nurses and attendants, every four days during their contact with patients. If a positive culture was obtained in a patient he was treated with a spray of dichloramin-T in chlorcosane. Physicians, nurses and attendants received this spray routinely every four hours.

Prophylactic Measures.—The following prophylactic measures were employed immediately on the diagnosis of meningitis being made: All contacts were isolated until negative throat cultures were reported. Any person having a positive culture was immediately isolated until three negative cultures, four days apart, were obtained. The throat was sprayed several times a day with dichloramin-T in chlorcosane. For the six hours preceding a throat culture the spray was not used.

Case 5 of this series illustrates the way in which contacts were followed up. The patient belonged to a hospital unit stationed at Fort McPherson. The entire unit of twelve officers and fifty men were immediately quarantined in their barracks and throat cultures taken. One officer, having left in the interval, was located and ordered to report to the department laboratory of the city in which he was;

* Submitted for publication Oct. 9, 1918.

a telegraphic report being sent by the department pathologist. One carrier was found in this unit, and immediately isolated until three negative cultures were obtained.

Physicians, nurses and attendants wore caps, gowns and masks when entering the patient's room. Physicians and nurses were not isolated when off duty, but attendants, who were not sufficiently trained in taking proper precautions, were isolated.

Our method of dealing with cases on reception at the hospital will be considered later.

Because of the marked variations of severity, symptoms and course presented by our cases, a brief description of each case is necessary before drawing our conclusions.

REPORT OF CASES

CASE 1.—The patient came by ambulance from Atlanta. He said that less than twenty-four hours before admission he had had a chill, with nausea, vomiting and headache and a temperature of 104 F. On admission he complained of pain in the chest, cough and fever; the cheeks were flushed. He was admitted as a case of lobar pneumonia.

Examination of the lungs was negative. Blood examination, next day: red blood corpuscles, 4,556,000; white blood corpuscles, 7,000; hemoglobin, 90 per cent.; differential: polymorphonuclears, 82 per cent.; for malaria, negative. His temperature, which was 104.6 on admission (pulse 100, respiration 28), in a few hours dropped to subnormal and remained there for four days. On the fifth day it went to 102.2; white blood cells, 23,800; 90 per cent. polynuclears. The next day, white blood cells 29,800. On the sixth day (November 30) he showed slight stiffness of the neck and a faintly positive Kernig. Lumbar puncture was done; spinal fluid appeared perfectly clear; unfortunately the tube was broken in transmission to the laboratory. Another lumbar puncture was made the next day (December 1); fluid cloudy; 20 c.c. of antimeningococcus serum were administered at once. The laboratory report showed "globulin, double plus; cell count 7,500; smear, very few gram-negative diplococci, some of which were intracellular; culture, hay bacillus (contamination)." From this time on the patient had fever, either intermittent or remittent. At times there was slight delirium. He complained a great deal of headache and morphin was necessary to control it. He was given in all, eleven intraspinal treatments; total, 232 c.c. of serum.

December 10, patient much better; temperature normal. December 11, temperature 102.6; he complained of severe headache and urticaria. In spite of the probability of this being due to the serum, we felt that the continued administration of serum was indicated. Serum was therefore given for the next two days and then discontinued as temperature returned to normal inside of twenty-four hours and the headache likewise disappeared. The urticaria persisted for about three or four days. The patient then made an uneventful recovery and after a month's leave of absence was returned to duty, Jan. 30, 1918.

CASE 2.—The patient complained of general pains all over the body, especially in neck and back. Temperature 101; pulse 110; respirations 26. On examination, his neck was somewhat rigid and attempts to elicit the Kernig sign produced slight pain in the back.

Lumbar puncture: fluid cloudy with decreased pressure, and when 12 c.c. were removed the patient complained of such excruciating headache that withdrawal of spinal fluid was stopped and 17 c.c. of serum administered. The introduction of the serum immediately stopped the headache.

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REPORT ON SPINAL FLUID

Date	Globulin	Cell Count	Smear	Culture
12/1	++	7,500	Polys., 87%; lymphs., 13%; very few gram-neg. intracellular diplococci	Hay bacillus (contaminated)
12/2	+	Colloidal gold 0-0-0-1-2-3-1-0-0-0
12/3	++	930	Polys., 65%; monos., 35%; occasional gram-neg. diplococci (intracellular)	Negative
12/4	Cells disintegrated; no micro-organisms found	B. subtilis
12/5	Wassermann anticomplementary
12/6	Colloidal gold 0-0-1-2-3-2-2-5-2-1
12/7	++	4,000	Polys., 86%; monos., 14%; numerous gram-neg. intracellular diplococci	Gram-neg. diplococci; no agglutination with polyvalent serum (antimeningitis)
12/8	1,400	Negative
12/9	++	5,700	Polys., 86%; monos., 14%; no micro-organisms	Negative
12/10	++	3,100	Polys., 74%; lymph., 26%	
12/11	+++	760	Polys., 82%; monos., 18%; no micro-organisms	
12/12	+	480	Polys., 18%; monos., 82%; no bacteria	Negative; colloidal gold, 5-5-5-3-2-2-2-1-1-1

REPORT ON INTRASPINOUS INJECTION OF SERUM

Date	Serum Given Intraspino- usly, C.c.	Fluid Withdrawn, C.c.	Date	Serum Given Intra- spino- usly, C.c.	Fluid Withdrawn, C.c.
12/1/17	22	25	12/ 7/17	20	30
12/2/17	30	30	12/ 8/17	20	30
12/3/17	20	30	12/ 9/17	20	30
12/4/17	20	30	12/10/17	20	30
12/5/17	20	30	12/11/17	30	30
12/6/17	20	30	Total	232	325

The patient was given six intraspino-
us injections, a total of 115 c.c. At
no time was the patient in bad condition or suffering severely. He made an
uneventful recovery.

On the eighth day, herpes labialis appeared. On the thirteenth day, serum
sickness occurred, with urticaria, but no rise in temperature.

CASE 3.—The patient (Pvt.) was admitted Dec. 15, 1917, with "German
measles." December 22 apparently well. December 23, was taken with vomit-
ing and headache, and soon became delirious; opisthotonos present and Kernig
positive; lumbar puncture: fluid cloudy; 18 c.c. of antimeningococcus serum
administered; nine doses of serum, once daily; total 168 c.c. administered.
The patient made an uneventful recovery. On the third day a profuse herpes
labialis appeared. Serum sickness occurred December 29, the seventh day,

a fine punctiform, erythematous rash appearing on the face, chest and back, which itched slightly; no headache, pains in joints, or fever. The fever was remittent and irregular, but not intermittent.

CASE 4.—The patient (Pvt.) was admitted at 6:30 a. m., Feb. 16, 1918, delirious and struggling. Three men were required to hold him; delirium so profound that he could not be aroused. The only history which could be obtained was that he had been taken with a violet headache at 2 a. m. the same day, and rapidly grew delirious. Temperature was 104, pulse 88, respirations 24. Physical examination was negative. There was no neck rigidity. Kernig was negative. Lumbar puncture was done at 9 a. m.; fluid cloudy; under some pressure; 20 c.c. of antimeningococcus serum administered. Patient grew weaker, and at 1 p. m. died suddenly. The spinal fluid showed globulin quadruple plus; cell count 8,000; smear 95 per cent. polys., monos., 5 per cent.; cells studded with gram-negative diplococci; culture showed meningococcus of intermediate Type 10. Necropsy showed characteristic lesions of the disease.

REPORT ON SPINAL FLUID

Date	Globulin	Cell Count	Smear	Culture
1/10	++++	8,000 (estimated)	Many very large gram-negative intracellular diplococci	Meningococcus; agglutination; para type
1/11	++++	15,900	Polys., 89%; monos., 11%; no meningococci seen	No growth
1/12	++	5,900	Polys., 95%; monos., 5%.....	Negative
1/13	++	980	No micro-organisms seen.....	Negative
1/14	++	520		
1/15	++	200	Polys., 40%; monos., 60%; no bacteria	Negative

REPORT ON INTRASPINOUS INJECTION OF ANTIMENINGOCOCCIC SERUM

Date	Serum Given Intraspino- usly, C.c.	Fluid Withdrawn, C.c.	Date	Serum Given Intra- spinously, C.c.	Fluid Withdrawn, C.c.
1/10	17	12	1/14	20	25
1/11	20	20	1/15	20	20
1/12	18	25			
1/13	18	25	Total	113	127

CASE 5.—Patient admitted Jan. 25, 1918; diagnosis, "suspected meningitis." On admission he was delirious; temperature 104. During the afternoon he complained of pains all over the body, especially back of head and neck. He worked until 6 p. m., and at 9 p. m. was in delirious condition; orthotonos, but no opisthotonos; Kernig negative. Lumbar puncture: fluid cloudy; 20 c.c. antimeningococcus serum was administered; treatment continued for three days; delirium disappeared, and the patient became quiet and rational. Temperature ranged from 98.6 to 100, and it was thought that he was beginning to convalesce. The next day his temperature rose, he became delirious and there was marked opisthotonos. One intraspinoous treatment was given daily for four days, during which time the patient grew steadily worse. His temperature increased and delirium became profound. He was so restless that it was found necessary to alternate morphin, $\frac{1}{4}$ grain, and chloral, 10 grains,

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sodium bromid, 20 grains, every two hours. Intraspinous treatments were increased to two a day. On the eleventh day of the disease an intravenous treatment of 50 c.c. of serum was given. The immediate effect was a rise in temperature. Six days later a second intravenous treatment was given, and four more the next four days. During all this time the two intraspinal treatments were given daily. The patient would always have a chill within an hour after treatment, with a rise of temperature to about 104. During this time he gradually grew better. The patient received treatments every day for twenty-two days; thirty-three intravenous treatments were given, a total of 675 c.c. of serum, and six intravenous injections, a total of 295 c.c., or a grand total of 970 c.c. of serum. Serum sickness occurred the tenth day after treatment was stopped, and the thirty-second day of the disease. The temperature had been normal for eight days. Serum sickness manifested itself by severe pains in the knees, most pronounced in the left knee, and by a temperature of 104.4.

REPORT ON SPINAL FLUID

Date	Globulin	Cell Count	Smear	Culture
12/23	++++	Disintegrated	Few gram-neg. biscuit-shaped diplococci; some intracellular	No growth
12/24	5,900	Polys., 92%; monos., 8%	
12/25	8,000		
12/26	++	1,700	Polys., 72%; monos., 28%; occasional gram-neg. extracellular diplococci	No growth
12/27	+	750	Polys., 55%; monos., 45%; no bacteria seen	No growth
12/28	+	60	Few disintegrated cells; no organisms.....	No growth
12/29	+	30	No growth
12/31	+	260	Streptococcus, gram-neg.

REPORT ON INTRASPINOUS INJECTION OF SERUM

Date	Serum Given Intraspino- usly, C.c.	Fluid Withdrawn, C.c.	Date	Serum Given Intra- spinously, C.c.	Fluid Withdrawn, C.c.
12/23	18	20	12/28	20	25
12/24	18	23	12/29	20	25
12/25	20	25	12/30	20	25
12/26	17	10	12/31	15	10
12/27	20	25			

Convalescence was very protracted and the patient is still (November 1) in the hospital, but is able to be up and around, though there is back and leg weakness. This postmeningitis asthenia, with spasticity of the legs, has been a feature lasting many weeks after the acute stage and deserves a special study and report.

CASE 6.—Patient (Pvt.) admitted Feb. 21, 1918, in a profound delirium of very acute onset; that is, less than twenty-four hours, and concerning which no history was obtainable. On admission he could not be aroused, struggled constantly, and had to be restrained. Temperature 100.2, pulse 54, respirations 20. Physical examination was negative; no neck rigidity and no Kernig;

lumbar puncture, fluid cloudy; 20 c.c. of serum administered; 20 c.c. intraspinal again administered within six hours of first dose; and 60 c.c. intravenously and two intraspinal treatments for next two days. His delirium had almost cleared up by this time and he was much improved. After one more intravenous and one more intraspinal treatment, the treatments were discontinued, although his temperature was above 102 for two days after the serum was discontinued. The patient made an uneventful recovery. Kidneys showed red blood corpuscles and hyaline, granular and blood casts. He had to be catheterized. On the ninth day, an erythematous rash appeared all over the body, followed by urticaria. There was no fever, headache or pain in joints.

CASE 7.—Patient (Pvt.) stepped on nail Feb. 14, 1918, making a superficial puncture on dorsum of left foot. Wound dressed and 15,000 antitetanic serum administered. He was kept in the post hospital. Three days later he had convulsions. Further history not obtainable. Thirty days later he was transferred to General Hospital No. 6, March 16, 1918, with a diagnosis of "(1) concussion of the brain or probable fracture of the skull, accidental; (2) meningitis traumatic; (3) pneumonia, lobar, left upper." The diagnosis on admission was "insanity, following traumatism, acute." History obtained from paternal uncle: "Father is a drunkard; one maternal aunt had epilepsy; three brothers and one sister are nervous, and patient was always considered feeble-minded."

Physical examination on admission showed that the patient was very weak and emaciated; beginning bed sore on right side; eyes protruding, movements free, pupils irregular, oval in outline, central and react sluggishly to light; some increase of intra-ocular tension; tongue dry and coated; knee jerks and ankle jerks markedly exaggerated; no Kernig; no Babinski; abdominal, cremasteric, biceps and triceps reflexes normal; heart, lungs, and abdomen negative. Mental examination: in bed; semiconfused; answers only after questions are repeated several times. Answers are fairly coherent; at times he is very noisy; speech is rambling, and he has acute hallucinosis; he wets and soils himself; lumbar puncture two days after admission; laboratory report on spinal fluid as follows: Wassermann, weakly positive at 0.5 c.c.; globulin double plus; cell count 180; colloidal gold 0-0-0-0-0-0-0-0-0-0-. Roentgenogram of heart, lungs and gallbladder negative. Urine showed a trace of albumin and many casts. Red blood cells, 4,800,000; white blood cells, 13,400; blood culture sterile.

The patient was also examined by the chiefs of the medical and surgical services and the head of the eye service. The eyegrounds were reported negative. The case was regarded as syphilitic meningitis or brain tumor. The patient's temperature was normal.

While in the hospital the patient gradually grew weaker and became greatly emaciated. Persistent vomiting soon developed and followed the taking of food. The temperature remained normal.

Examination April 18, 1918, thirty-three days after admission revealed the following: heart sounds very weak; pulse 116; left patellar reflex normal; right slightly decreased; neck not as flexible as one would expect from a semicomatose patient, though not markedly rigid; well-marked *taché*. Lungs negative. The possibility of a tuberculous meningitis was also considered, and it was planned to examine the spinal fluid for tubercle bacilli, but before this was done the patient died, after being under our care thirty-seven days and in the post hospital before coming here thirty days.

Necropsy showed the ventricles of the brain greatly distended with a semipurulent fluid in which the meningococcus was present. (Internal hydrocephalus, bilateral); meningitis (meningococcus.) The spinal canal was

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REPORT ON SPINAL FLUID

Date	Cell Count	Globulin	Smear	Culture
1/25	5,000	++++	Many pus cells; gram-neg. intracellular diplococci	Gram-pos. bacillus; probably contam.
1/26	6,000	Few atypical gram-neg. diplococci	
1/27	1,800	Polys., 90%; monos., 10%; no organisms seen	Negative
1/28	2,100	No bacteria	
1/29				
1/30	700	+	No organisms found.....	Negative
1/31	3,800	++	Few extracellular gram-neg. diplococci....	Negative
2/ 1	1,800	++	No organisms seen.....	Negative
2/ 2	1,100	+	Polys., 70%; monos., 30%; no organisms seen	Negative
2/ 5	820	+	No organisms seen.....	Negative
2/ 6	280	+	No organisms seen.....	Negative
2/ 6	over 1,000	No organisms seen	
2/ 7	330	+	Polys., 85%; monos., 15%; no organisms	Negative
2/ 8	170	+++	Many gram-neg. cocci resembling meningococci	Negative
2/ 9	1,560	++	No organisms found.....	Staphylococcus albus (Strepto.)
2/10	1,600	++++	No organisms found.....	B. subtilis
2/12	720	+++	No organisms seen.....	B. subtilis
2/14	70	++++	Cells disintegrated; no organisms seen....	Negative

Blood culture, Feb. 11, 1918, sterile.
 Blood count, Feb. 15, 1918, red blood cells, 4,270,000; white blood cells, 1,700; polymorphonuclears, 86 per cent.; mononuclears, 14 per cent.

REPORT ON INTRASPINOUS AND INTRAVENOUS INJECTION OF SERUM

Date	Serum Given Intraspino-ously, C.c.	Fluid With-drawn, C.c.	Serum Given Intraven-ously, C.c.	Date	Serum Given Intraspino-ously, C.c.	Fluid With-drawn, C.c.	Serum Given Intraven-ously, C.c.
1/25	20	17		2/ 8	20	50	
1/26	20	30		2/ 8	20	60	
1/27	20	25		2/ 9	20	55	
1/28	20	10		2/ 9	20	60	
1/29	20	8		2/10	20	46	
1/30	20	25		2/10	20	45	40
1/31	20	40		2/11	30	60	
2/ 1	20	38		2/11	25	50	50
2/ 2	20	60		2/12	20	60	
2/ 3	20	45		2/12	20	60	50
2/ 3	20	60		2/13	20	60	
2/ 4	20	45		2/13	20	60	45
2/ 4	20	67	50	2/14	20	40	
2/ 5	20	60		2/14	20	60	60
2/ 6	20	70		2/15	20	60	
2/ 6	20	70			675 295	1,706	295
2/ 7	20	70		Total serum given.....	970		
2/ 7	20	70					

occluded so that the meningeal fluid did not freely enter the spinal canal. Puncture of the cisterna magnum should have been done had the possibility of this occlusion occurred to us.

REPORT ON SPINAL FLUID

Date	Globulin	Cell Count	Smear	Culture
2/21	R. B. C. pus, and some gram-neg. bacilli; no meningococci observed	
2/22	++++	39,000	Many pus cells; gram-neg. intracellular diplococci	Meningococcus — normal agglutinates: 1:400 with normal antiserum; 1:100 with intermediate antiserum; no agglutination with para antiserum; 1:200 with polyvalent antiserum

REPORT ON INTRASPINOUS AND INTRAVENOUS ADMINISTRATION OF SERUM

Date	Serum Given Intraspinozously, C.c.	Fluid Withdrawn, C.c.	Serum Given Intravenously, C.c.
2/21	20 25	30 40	60
2/22	20 20	50 15	
2/23	20 20	35 12	
2/24	20	3	55
Total	145	185	115

CASE 8.—Patient was admitted April 18, 1918, from war prison barracks, with a diagnosis of suspected spinal meningitis. He was semidelirious; complained of severe headache, pain in neck and back and vomiting. There was marked opisthotonos. The temperature was 97.6 F., pulse 76, respirations 20. Lumbar puncture clear, under normal pressure. The clinical signs being so marked, 20 c.c. of antimeningococcus serum were given. Laboratory report: spinal fluid, globulin negative; cell count 50; smear negative; culture meningococcus.

The patient was given two intraspinozous treatments daily for three days, and then one daily for four days. It was necessary to chloroform him for all of his treatment as he struggled so violently.

At the end of this time it was felt that he was not making satisfactory progress. There was a profound delirium, weak, irregular pulse, and stimulation was necessary for the heart. The temperature was 103.8 and the patient complained incessantly of excruciating pains in the head. The next day the patient was given two intraspinozous treatments and one intravenous treatment of 50 c.c. He had a chill and temperature rose to 104.8 and urticaria appeared. The next morning the temperature was normal and remained practically normal all day. All serum treatment was discontinued and patient made an uneventful recovery, the temperature never being more than 1 degree above normal.

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REPORT ON SPINAL FLUID

Date	Globulin	Cell Count	Smear	Culture
4/19	Neg.	50	Negative.....	Meningococcus
4/19	++	2,850	Pus and some partially autolyzed organism, probably meningococci	
4/20	++	1,725	Some pus cells; no organisms.....	Negative
4/21	++	2,200	Not done.....	Not done
4/22	++	1,300	Not done.....	Not done
4/22	+++	500	Not done.....	Not done
4/25	++	3,400	Not done	

April 27: White blood cells, 11,100; polymorphonuclears, 82 per cent.; mononuclears, 18 per cent.

REPORT ON INTRASPINOUS AND INTRAVENOUS ADMINISTRATION OF SERUM

Date	Serum Given Intraspino- usly, C.c.	Fluid With- drawn, C.c.	Serum Given Intra- venously, C.c.
4/19	20	30	
4/19	20	30	
4/20	20	30	
4/20	20	20	
4/21	20	50	
4/21	20	50	
4/22	30	30	
4/23	..	50	
4/24	20	40	
4/25	24	60	
4/26	30	40	
4/26	30	40	
4/26	50
Total	274	470	50

Blood count April 27, 1918: white blood cells 11,000, polymorphonuclears 82 per cent., mononuclears 18 per cent. June 28, 1918, this patient had recurrence of meningitis which ran a course similar to the initial attack and from which he recovered.

CASE 9.—The patient (Pvt. J.), who was admitted from Camp Gordon with a diagnosis of "fever, type undetermined," said that while on a hike two days before his left arm and side began to feel numb, with pain in shoulders and back of neck. On admission he seemed in fairly good condition; complained of pain in back and soreness in the back of neck. There was also a "catchy" pain over the heart at times. Physical examination showed a few râles at base of left lung, with bronchial breathing over left upper lobe.

There was slight tenderness over left side of abdomen. The temperature was 100.4, pulse 80, respirations 20. First diagnosis, "influenza."

April 20, 1918, thirteen days later, the temperature was 104, pulse 104, respirations 28, with nausea, vomiting, rigidity and tenderness over right side of abdomen. He was seen by the surgical service as a possible case of appendicitis. Blood showed white blood corpuscles 32,800; Examination for malaria was negative. Headache developed, with pain and stiffness of neck and slight Kernig.

April 22, the temperature was 102.8, pulse 86, respirations 28. Lumbar puncture under chloroform secured a cloudy fluid. Twenty c.c. of antimeningococcus serum were given. The next day two intraspinous treatments were given, and then one daily for three days. Four days after the last serum and eight days after first serum was given, the patient broke out with urticaria. He made an uneventful recovery.

REPORT ON SPINAL FLUID

Date	Globulin	Cell Count	Smear	Culture
4/22	++	6,100	Pus and a few extracellular gram-negative diplococci	Negative
4/23	++	2,700	Not done.....	Not done

REPORT ON INTRASPINOUS INJECTION OF SERUM

Date	Serum Given Intraspiously, C.c.	Fluid Withdrawn, C.c.	Date	Serum Given Intraspiously, C.c.	Fluid Withdrawn, C.c.
4/22	20	50	4/25	20	40
4/23	20	60	4/26	30	40
4/23	20	50			
4/24	20	25	Total	130	205

CASE 10.—The patient (Pvt.) who was admitted April 9, 1918, with a diagnosis of "influenza," for two days prior to admission complained of fever, headache and pain across the abdomen, extending to back; similar complaint on admission. Physical examination was negative, except for a slight pharyngitis. Temperature on admission, 102.2; normal in four days, when patient appeared to be convalescing. April 22, thirteen days after admission, he had a chill after supper. The temperature rose to 104, pulse 86, respirations 20. His temperature next morning was 100.6. He complained of headache, pain in back of neck and generalized pain in abdomen. Opisthotonos was present and Kernig faintly positive, yet his answers were so contradictory, and he was so frightened when examined that one felt doubtful about the signs. Lumbar puncture fluid was purulent. The laboratory report showed pus cells and thousands of meningococci. Twenty c.c. of antimeningococcus serum were administered. At this time the temperature was 104, pulse 160, and respirations 36, the two latter probably due to fright. The next day the temperature was subnormal all day. One intravenous treatment of 50 c.c. was given, and intraspinous treatments, one of 20 c.c., and some of 40 c.c. Two intraspinous treatments were given daily for two days more. The temperature gradually increased up to 101. Treatment was then omitted for three

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days, when one intraspinal injection of 15 c.c. was given. April 30, the patient had a chill, with rise of temperature to 103.6, but during the next three days it returned to normal, and the patient made an uneventful recovery.

April 28, he complained of pain in the left ankle; May 1, pain in both ankles; May 2, orchitis, left. There was no rash or rise of temperature.

REPORT ON SPINAL FLUID

Date	Globulin	Cell Count	Smear	Culture
4/23	++	400	Pus and thousands of meningococci	Meningococcus

REPORT ON INTRASPINOUS AND INTRAVENOUS ADMINISTRATION OF SERUM

Date	Serum Given Intraspinaly, C.c.	Fluid Withdrawn, C.c.	Serum Given Intravenously, C.c.
4/23	20	40	50
4/24	20	50	
4/24	40	60	
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4/25	16	35	
4/25	20	50	
4/26	20	50	
4/26	30	40	
4/30	15	40	
Total	181	378	50

SUMMARY

Our experience and conclusions may be summed up as follows:

Ten cases of epidemic cerebrospinal meningitis were treated. Two men died, one an extremely fulminating case, who lived less than twelve hours after the onset and who received an intraspinal treatment of 2 c.c. of antimeningococcus serum; the other, an unrecognized and untreated case in which the man lived sixty-seven days, and in which diagnosis was either a syphilitic or tuberculous meningitis, and in which necropsy revealed a walled-off meningococcus infection of the brain.

The physical signs at the onset; that is, when first examined at the hospital, were as follows:

Kernig sign was present in 5 cases, or 50 per cent.; opisthotonos was present in 3 cases, or 30 per cent.; orthotonos was present in two cases, or 20 per cent.; delirium was present in 6 cases, or 60 per cent.; headache was present in 8 cases, or 80 per cent. (in the

other two cases the history was not obtainable); fever was present in eight cases, or 80 per cent. (in four of these cases the temperature was 104 or more).

The pulse was slow in comparison to the temperature, only one case showing the pulse above 103. Respirations were slightly increased. In 5 it was 20, and the other 5 ranged from 22 to 30. Vomiting was present in 6 cases, or 60 per cent. Lumbar puncture showed a cloudy fluid in 7 cases, or 70 per cent. In 3 cases, or 30 per cent., it was clear. A chill occurred in 3 cases, or 30 per cent.

During the course of the disease, the following findings were recorded: Serum sickness occurred in every treated patient except two, and one of these lived only four hours after his first treatment. The other patient was a negro, and he developed pain in ankles and testicles, and there was no rash. Of the six cases in which opisthotonos was absent at the onset, it developed later in two. Orthotonos was a common feature.

Of the five cases in which the Kernig sign was absent at the onset, it developed in two. Herpes labialis occurred in three cases, or 30 per cent. Purpura and rash, except that from serum sickness, was absent in all cases. The "spotted" rash described as one of the features of this disease did not occur in any of our cases. Three patients, or 30 per cent., required catheterizing. All patients ran a febrile temperature.

CONCLUSION

In conclusion, we would like to emphasize the following points: The cases here reported showed no uniformity of symptoms or signs. Marked variations of symptoms was the rule. Those symptoms and signs which in our cases appeared with the greatest uniformity were as follows: headache 100 per cent., fever 80 per cent., delirium 60 per cent., vomiting 60 per cent., Kernig 50 per cent., opisthotonos 30 per cent., orthotonos 20 per cent.; but no cases presented the hemorrhagic spinal "spotted" rash. In connection with the latter we have questioned whether the early administration of serum prevented the meningococcus from producing widespread toxic effects. Certainly, the prompt improvement following administration of serum supports such a theory, as indicated by the majority of our cases. If the "spotted" rash heretofore described as characteristic of this disease is due to hemolysis from an associated hemolytic streptococcus, one would be disposed to conclude that its absence in those patients treated early was due to the prevention of toxemia. If the petechial rash were due to septic emboli, these too would be associated with a similar toxemia checked by early serum treatment. Two of our patients showed no signs except fever and delirium.

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The early diagnosis of this disease is of the greatest importance, as danger of infection of others is thereby lessened, and by early treatment the patient has the best chance of recovery. In many cases, early diagnosis is only possible by lumbar puncture and examination of the spinal fluid. Therefore, all doubtful cases should receive lumbar puncture, which, if properly done, is a comparatively simple, and a relatively safe procedure. Cases of fever and delirium with no other physical signs should have this done. When performing a lumbar puncture, *one should have everything ready to administer serum. If the spinal fluid is cloudy, or if clear with physical signs of meningeal involvement, give 20 or 30 c.c. of antimeningococcus serum.*

Not only is early treatment important, but intensive treatment should be started at once. Two intraspinal treatments of from 20 to 30 c.c. should be given every twenty-four hours. The intraspinal treatments should be given thus for the first few days, and decreased as the patient improves clinically.

As to the use of intravenous treatment, while we do not feel justified in drawing any conclusions, our feeling has been that all patients who come in with marked toxic symptoms, and all who are doing badly, should be thus treated. Fifty or 60 c.c. are given intravenously as often as once in every twenty-four hours, following the method of Cole. Very commonly a chill, followed by a rise of temperature to 103, 104, or even 105, occurs, but this is often followed by a drop to normal or even subnormal, and should cause no alarm. Herrick* reported the successful use of intravenous meningococcus serum at Camp Jackson. Herrick's report brought out valuable discussion to which the reader is referred.

Case 8 indicates that the intravenous treatment will at times bring about favorable results when the intraspinal method seems to fail.

As to when all serum therapy should be discontinued, it is very difficult to decide. In this connection the temperature is of practically no value as a guide. Normal or subnormal temperature may be present at the onset or during the first few days, while fever may be due to the effect of the serum. The two most reliable guides are the *spinal fluid* and the *general condition of the patient*. Treatment should not be discontinued until the spinal fluid is clear and free from meningococci, and not until the patient is clearly in much better condition, free from delirium and toxic signs. Serum sickness, which was present in practically all of our cases, may cause headache and fever and be mistaken for actual symptoms of the disease itself. The presence of a rash, usually urticaria, and pain in the joints, will often serve to differentiate the two.

* Proceedings of Assn. Am. Phys., May, 1918, to be published.

A safe way is to omit serum treatment for one day, then for two days, and if the patient continues to improve, discontinue it entirely.

One thing to bear in mind is that serum is the only method of treatment, and that if properly administered it cannot cause any permanent symptoms. Serum sickness is not a contra-indication to further treatment. Therefore, give serum as soon, as frequently, and in as large doses as possible.

The method of serum administration we used was as follows: The patient lies on his side, with his back at the edge of the bed. The knees and hips are flexed as far as possible, and the back bowed out. Opisthotonos increased the difficulty of successful puncture. Often $\frac{1}{4}$ grain of morphin, one-half hour before treatment would relax and quiet the patient. In some cases it was necessary to use chloroform. The operator should wear gloves to protect both himself and the patient. The amount of fluid that should be removed varies not only in individual cases but in the same case from day to day. "With the spinal fluid under pressure I (Bowman) have twice removed 70 c.c. in twenty-four hours. In some cases with decreased pressure, I (Bowman) have been unable to remove more than 12 c.c. because of the patient's complaining of such excruciating headache." In these latter cases, injection of the serum immediately caused a disappearance of the headache. Usually from 20 to 30 c.c. of serum was given intraspinaly, 40 c.c. being the largest dose. If the serum would not flow freely, slight pressure from a syringe was used to force it in.

For the extreme delirium, morphin and chloral may be used freely. When one realizes the energy a restless, delirious patient uses up every twenty-four hours, and the long-drawn-out character of the disease in some cases, it seems wise to save the patient's energy as well as to make him comfortable by the use of these drugs.

The diet must not be neglected. It is common to order "liquid diet" for febrile and delirious patients. The high caloric diet as in typhoid should also be applied to meningitis. We found that one overactive, delirious patient who was twisting and turning in bed night and day and talking incessantly, was using twice the energy of the average well man, and was receiving less than 1,000 calories a day. After a conference with our dietitian, Miss de Garmo, a special diet was arranged for all our patients, which, of course, varied a great deal in individual cases, but which averaged from 2,000 to 2,500 calories. Attention to or neglect of this may turn the scale in desperately ill patients.

Bladder distention should be watched for in all delirious patients. In one of our cases, incontinence with retention occurred, and was

DATA OF AUTHORS' CASES

	Case									
	1	2	3	4	5	6	7	8	9	10
Kernig at onset.....	0 developed later	+	+	0	0 developed later	0	0	++	+	+
Opisthotonos at onset.....	0 developed later	0	+	0	0 developed later	0	0	++	+	+
Orthotonos.....	0	+	..	0	+	0	?			
Temperature at onset.....	104.6	100.0	101.0	104.0	104.0	100.2	99.0	97.6	100.4	104.0
Pulse at onset.....	100	102	116	88	80	54	80	76	80	86
Respiration at onset.....	28	22	30	24	24	20	20	20	20	20
Delirium at onset.....	0 later	0	+	+	+	+	+	+	0	?
Headache at onset.....	+	+	+	+	+	?	?	+	+	+
Vomiting at onset.....	+	0	+	0	0	0	+	+	+	+
Serum sickness.....	+	+	+	0	+	+	0	+	+	?
Appearance of fluid at first puncture.....	Clear	Cloudy	Cloudy	Cloudy	Cloudy	Cloudy	Clear	Clear	Cloudy	Cloudy
First puncture— Cell count.....	7,500	8,000	?	8,000	5,000	Pus	180	50	6,100	400
Globulin.....	++	+++++	+++++	+++++	+++++	+++++	++	0	++	++
Smear.....	Menin. (87% Poly.)	Many para- menin.	Menin. + No growth	Menin. +	Menin. 0	Menin. 0	Not done	Menin. 0	Menin. +	Menin. +
Culture.....	Hay bac.	Menin. +	Menin. 0	Menin. 0	Not done	Menin. +	Menin. 0	Menin. +
Amount serum given, C.c.	232	114	168	20	675 S + 295 V = 980	145 S + 115 V = 260	0	274 S + 50 V = 324	130	181 S + 50 V = 231
Number of treatments.....	11	6	9	1	33 S + 6 V = 39	7 S + 2 V = 9	0	13 S + 1 V = 14	6	8 S + 1 V = 9
Outcome.....	Cured	Cured	Cured	Died	Cured	Cured	Died	Cured	Cured	Cured
Herpes.....	+	+	0	0	0	0	0	0	0	0
Chill at onset.....	+	Chilliness	0	?	0	?	0	0	0	+

only relieved by catheterization. Attendants and nurses should be cautioned to report slight incontinence of urine, as it may be an important index of retention. The urine should be carefully measured. In delirious cases, retention of urine may greatly add to the restlessness of the patient.

An accident which occasionally occurs is the *breaking of the needle* in the spinal column. This occurred in one of the earlier cases treated at this hospital, and has occurred at other military hospitals. In our case a subsequent operation successfully removed the fragment of the needle and at no time were there any ill effects. This risk is now overcome by using a needle made of a metal which is *bendable* but not breakable.

It has been found helpful to place on the wall *in consecutive order* the temperature charts, record of serum and blood examination and the daily record of calories taken and the amounts of serum given. This is a simple clinical point, but when the fight with the disease is at its height, the map of the operation offers a quick and graphic way of determining how the fight is going and enables the physician to direct his forces.

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FURTHER STUDIES CONCERNING THE ESSENTIAL
NATURE OF ANTITRYPTIC ACTIVITY OF NORMAL
SERUM AND THE PHYSIOLOGIC FUNCTION
OF PANCREATIC FERMENTS*

H. WAGO, M.D.
CHICAGO

A. REVIEW OF THE LITERATURE ON THE ANTITRYPTIC
ACTION OF NORMAL SERUM

We have records of a great number of experimental observations on the antitryptic power of normal serum. The significance of this antitryptic power, however, has not yet been determined.

The power that normal serum possesses for preventing the action of trypsin, so far as I have been able to learn, was first definitely noticed by Hahn,¹ in 1897, who said that this action disappeared on heating after at from 65 to 70 C. Fermi and Pernossi,² in 1894, had noticed that trypsin rapidly disappeared after injection into the animal body, and that it was destroyed by contact with the tissues in vitro. On the significance of this power, Landsteiner,³ in 1900, stated that the anti-action of serum against trypsin was intimately connected with the albumin fraction, after coming down between half and full saturation of the serum with ammonium sulphate. Oppenheimer and Aron,⁴ in 1903, also observed that the resistance of serum to trypsin digestion depends on the configuration of the protein molecules; but, on the other hand, Glaessner,⁵ in 1903, contradicted Landsteiner's observation, and concluded that it was associated with the euglobulin, that is, the fraction precipitated by one-third saturation with ammonium sulphate. In 1904, however, Cathcart⁶ proved Landsteiner's observation, and also that globulin does not possess antitryptic action, that absolute specificity does not exist and that this anti-action is effected by heating for 30 minutes at 60 C. in the presence of alkali, and at about 70 C. in its absence. Delezenne and Pozarski,⁷ in 1903, found

* Submitted for publication Oct. 1, 1918.

* From the Laboratory of Preventive Medicine, University of Chicago.

1. Hahn: Berl. klin. Wchnschr., **34**: 1897.

2. Fermi and Pernossi: Ztschr. f. Hyg., **18**: 1894.

3. Landsteiner: Centralbl. f. Bakt., **27**, Nos. 10 and 11, Abt. 1, 1900.

4. Oppenheimer and Aron: Hofmeisters' Beitr. z. chem. Phys. u. Path., **4**: 1903.

5. Glaessner: Hofmeisters' Beitr. z. chem. Phys. u. Path., **4**: 1903.

6. Cathcart: Jour. Physiol., **31**: 1904.

7. Delezenne and Pozarski: Compt. rend. Soc. de biol., **55**: 1903.

and other diseases with cachexia can be thus explained; he also found that this activity decreases during fastings, and increases during digestion. These facts were proved by Franz and Jarisch²³ in 1912. Meyer,²⁴ in 1911, does not believe that protein cleavage products are the inhibiting agents. He believes that antitrypsin is a true antibody, and that the ferment of tissue cells acts as antigen. In this year,

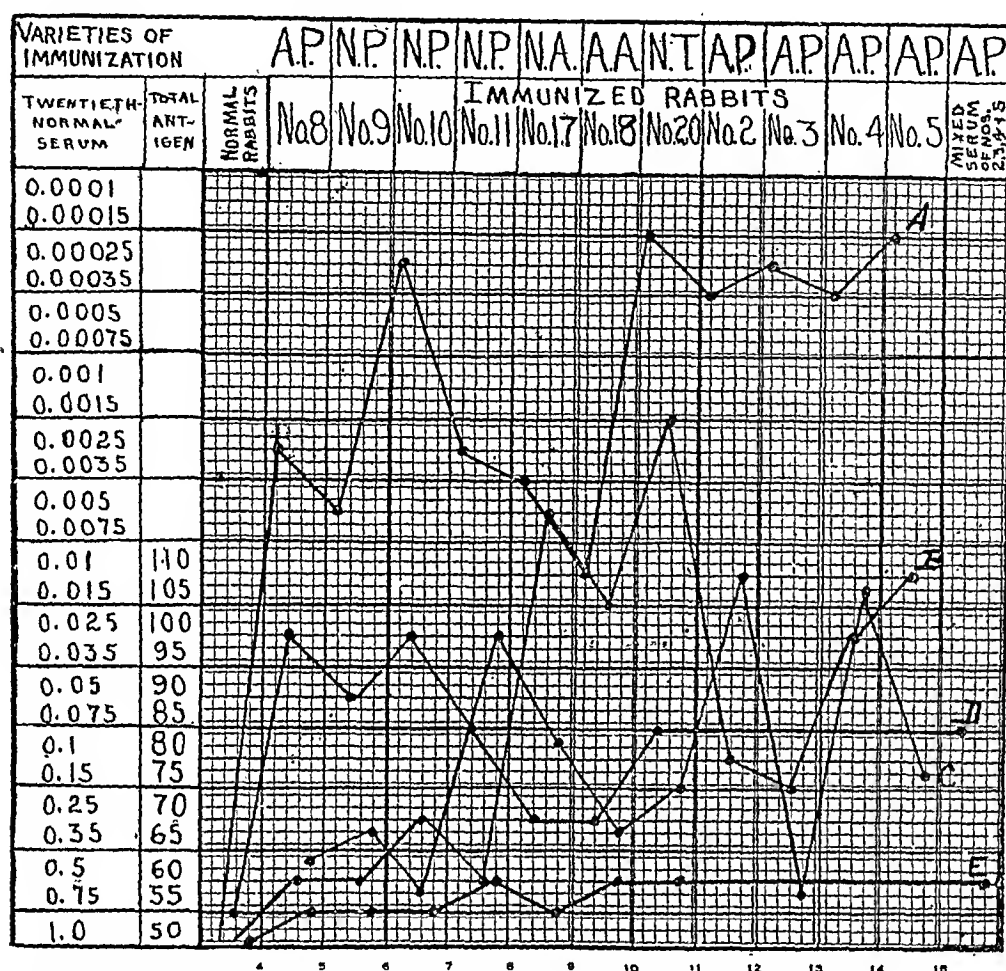


Chart showing the relation between the production of antibodies and the antitryptic action of serum. A. P.=alcoholic pancreatin; N. P.=native pancreatin; N. A.=native amylopsin; A. A.=alcoholic amylopsin; N. T.=native trypsin; A line= precipitation; B line= complement deviation; C line= total amount of antigens; D line= complete digestion of fibrin; E line= partial digestion of fibrin.

Weiberg and Ruenstein²⁵ found that ultraviolet rays destroyed the antitryptic substance in human serum. Rubenstein²⁶ also observed that the antitryptic power disappeared by heating at 70 C. In 1912, Abderhalden²⁷ found that during pregnancy there developed in the

23. Franz and Jarisch: Wien. klin. Wchnschr., 25: 1912.

24. Meyer: Folia serolog., 7: 1911.

25. Weiberg and Rubenstein: Compt. rend. Soc. de biol., 71: 1911.

26. Rubinstein: Compt. rend. Soc. de biol., 71: 1911.

27. Abderhalden: München. med. Wchnschr., 59: 1912.

blood specific enzymes for digesting placenta proteins. The blood of a pregnant woman shows constantly an increased antitryptic power. In 1914, Bronfenbrenner²⁸ observed that any normal serum placed in contact with "sensitized" placenta acquired the same property. Therefore, it might be surmisable that the Abderhalden reaction would be composed of two phases: the one specific for the sensitization of placenta, the other nonspecific for the autodigestion of the serum as a result of the presence of sensitized placenta; and he²⁹ also said that the specificity of the Abderhalden reaction depends not as Abderhalden believed, on the presence of specific enzymes, but on the presence in the blood of pregnant women of a specific antibody that combines with placenta antigen and thus sets free the only proteolytic enzymes which is always present in the normal serum. In 1913, Kirchheim³⁰ concluded that the antiferment merely prolongs the action of the trypsin and does not destroy it, confirming Bayliss and Starling's experiments. He also found chloroform reduced the inhibiting action of the serum as Delezenne and Pozarski's experiments proved. Sugimoto,³¹ in 1913, observed that there was a decrease in the antitryptic strength of serum after the serum had been extracted with ether and benzol. He concluded that the lipoids were the active constituents. Confirming Schwartz, he believed also that a complete extraction of fat and the dissociation of the lipoid-protein combinations will cause a removal of the ferment inhibiting action. In this year we have a critical discussion on the significance of antitryptic action of normal serum by Kämmerer,³² Kämmerer and Aubry,³³ and Rosenthal.³⁴ Kämmerer contradicted Rosenthal's theory and asserted that the globulin fraction is inhibited like the albumin fraction. This antitryptic action is affected at 56 C. Rosenthal was opposed to Kämmerer's theory, but in 1914, Jobling and Petersen³⁵ observed that the ferment-inhibiting substances of the serum are lipoids corresponding to Schwartz's and Sugimoto's observation, and that they are in fat solvents, and lose their ferment inhibiting action when heated with serum at 70 C., similar to Rubenstein's observation.

On the antitrypsin in pathologic serum, Brieger and Trebing,³⁶ in 1908, found that it increases in carcinoma and sarcoma, and this was proved by Bergmann and Meyer.³⁷ Bergmann and Bamberg¹⁴

28. Bronfenbrenner: *Proc. Soc. Biol. and Med.*, **12**: 1914, No. 1.

29. Bronfenbrenner: *Biochem. Bull.*, **4**: 1915.

30. Kirchheim: *Arch. f. exper. Path. u. Pharmakol.*, **73**: 1913.

31. Sugimoto: *Arch. f. exper. Path. u. Pharmakol.*, **74**: 1913.

32. Kämmerer: *München. med. Wchnschr.*, **60**: 1913.

33. Kämmerer and Aubry: *Biochem. Ztschr.*, **48**: 1913.

34. Rosenthal: *München. med. Wchnschr.*, **60**: 1913.

35. Jobling and Petersen: *J. Exper. Med.*, **19**: 1914.

36. Brieger and Trebing: *Berl. klin. Wchnschr.*, 1908, Nos. 22, 29 and 45.

37. Bergmann and Meyer: *Berl. klin. Wchnschr.*, 1908, Nos. 37 and 45.

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found antitrypsin not only in carcinoma and sarcoma, but present in acute infections and chronic diseases such as pneumonia, typhoid fever, tuberculosis, syphilis, chronic anemia, basedow, amebic dysentery, pancreas necrosis of men, and various sicknesses.

On the significance of antitryptic action of normal serum, therefore, we have at present no definite agreement. This important subject stimulated my interest and I have followed it up in the experiments to be described.

B. ON THE INHIBITION OF NORMAL SERUM AGAINST PANCREATIC DIGESTION

EXPERIMENT 1.—*The Inhibiting Action of Normal Ox, Sheep, Rabbit and Guinea-Pig Serum against Fibrin Digestion by Pancreatin.*—For this examination the following materials were used: (a) Half-normal serum of 5 oxen, 5 sheep, 8 rabbits and 6 guinea-pigs; (b) one c.c. of a 1 per cent. pancreatin salt solution filtered through a Berkefeld filter added to every tube, which contained half-normal serum; (c) carmin-stained oxfibrin about the size of an apple seed.

TABLE 1.—INHIBITING POWER AGAINST PANCREATIN DIGESTION OF NORMAL RABBIT SERUM

Results in 24 hours at 38 C. with 1 c.c. of 1 per cent. pancreatin

Half-Normal Serum, C.c.	Rabbit 1	Rabbit 2	Rabbit 3	Rabbit 4	Rabbit 5	Rabbit 6	Rabbit 7	Rabbit 8
0.35	0	0	±	0	0	±	0	0
0.25	++	++	+++	+++	+++	+++	++	+++
0.15	+++	++++	++++	++++	++++	++++	+++	++++
0.1	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.
0.075	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.

In this and following tables 0 denotes a negative for fibrin digestion; ± = trace (very slight digestion); + = slight digestion (partial); ++ = medium digestion; +++ = marked digestion; Comp. = complete digestion; ++++ = almost complete digestion.

TABLE 2.—THE INHIBITING POWER AGAINST PANCREATIN DIGESTION OF NORMAL OX SERUM

Results in 24 hours at 38 C. with 1 c.c. of 1 per cent. pancreatin

Half-Normal Serum, C.c.	Ox 1	Ox 2	Ox 3	Ox 4	Ox 5
0.35	0	0	0	0	0
0.25	0	0	0	0	0
0.15	++	+++	++	+++	+++
0.1	++++	++++	++++	+++	++++
0.075	Comp.	Comp.	Comp.	Comp.	Comp.

TABLE 3.—THE INHIBITING POWER AGAINST PANCREATIN DIGESTION OF NORMAL SHEEP SERUM

Results in 24 hours at 38 C. with 1 c.c. of 1 per cent. pancreatin

Half-Normal Serum, C.c.	Sheep 1	Sheep 2	Sheep 3	Sheep 4	Sheep 5
0.35	0	0	0	0	0
0.25	0	0	0	0	0
0.15	+++	+++	+++	++	+++
0.1	++++	Comp.	++++	+++	Comp.
0.075	Comp.	Comp.	Comp.	Comp.	Comp.

TABLE 4.—THE INHIBITING POWER AGAINST PANCREATIN DIGESTION OF NORMAL GUINEA-PIG SERUM

Results in 24 hours at 38 C. with 1 c.c. of 1 per cent. pancreatin

Half-Normal Serum, C.c.	Pig 1	Pig 2	Pig 3	Pig 4	Pig 5	Pig 6
0.35	0	0	0	0	0	0
0.25	0	0	0	0	0	0
0.15	0	0	0	0	0	0
0.1	++	+++	++	++	+++	++
0.075	+++	+++	++++	+++	++++	+++
0.05	Comp.	++++	Comp.	Comp.	Comp.	++++
0.035	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.

The results in Tables 1 to 4, inclusive, show that normal animal serum has an inhibiting power against pancreatin digestion of oxfibrin, but the extent of this inhibiting power differs appreciably in the different animals. In my experiment 0.35 c.c. of half-normal rabbit serum inhibited completely fibrin digestion with 1 c.c. of a 1 per cent. pancreatin, 0.25 c.c. of a ox and sheep half serum and 0.15 c.c. of a guinea-pig half serum.

On the neutralization of the inhibiting power of normal serum against trypsin, Achalme and Stevenin,³⁸ in 1911, stated that 0.01 or 0.015 c.c. of trypsin neutralized 0.006 c.c. of human serum, 0.015 c.c. of rabbit serum and 0.01 of guinea-pig serum. My experiments with regard to the amount of pancreatin necessary for the neutralization of the inhibiting power of normal rabbit, ox, sheep and guinea-pig serum against pancreatin differ very much from those of Achalme and Stevenin in their results, as shown in the foregoing tables: 0.35 c.c.

38. Achalme and Stevenin: Compt. rend. Soc. de biol., 1911, 70, No. 12.

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of rabbit half serum, 0.25 c.c. of ox and sheep half serum and 0.15 c.c. of guinea-pig half serum were neutralized completely by 1 c.c. of a 1 per cent. pancreatin. Therefore, 0.1 c.c. of rabbit serum is necessary to neutralize 0.006 of pancreatin, 0.1 c.c. of ox and sheep serum neutralizes 0.008 of pancreatin, and 0.1 c.c. of guinea-pig serum neutralizes 0.013 of pancreatin. The inhibiting power of guinea-pig serum, therefore, is the strongest among the serums, such as ox, sheep and rabbit serum, the rabbit serum being the weakest.

EXPERIMENT 2.—*Effect of Heat on the Inhibition of Normal Ox, Sheep, Rabbit and Guinea-Pig Serum against Fibrin Digestion by Pancreatin.*—The technic for fibrin digestion by pancreatin in this experiment was just the same as in Experiment 1, but the quantity of 1 per cent. pancreatin used was 0.35 c.c. to each tube.

TABLE 5.—THE EFFECT OF HEAT ON THE INHIBITION OF NORMAL RABBIT SERUM AGAINST PANCREATIC DIGESTION

Results in 24 hours at 38 C. with 0.35 c.c. of 1 per cent. pancreatin

Half-Normal Serum, C.c.	Unheated Serum	Heated Serum, 56 C. 30'	Heated Serum, 65 C. 30'
1.0	0	0	Comp.
0.75	0	0	Comp.
0.5	0	±	Comp.
0.35	0	++++	Comp.
0.25	0	Comp.	Comp.
0.15	0	Comp.	Comp.
0.1	+	Comp.	Comp.
0.075	Comp.	Comp.	Comp.
0.05	Comp.	Comp.	Comp.

TABLE 6.—THE EFFECT OF HEAT ON THE INHIBITION OF NORMAL OX AND SHEEP SERUM AGAINST PANCREATIC DIGESTION

Results in 24 hours at 38 C. with 0.35 c.c. of 1 per cent. pancreatin

Half-Normal Serum, C.c.	Unheated Serum	Heated Serum, 56 C. 30'	Heated Serum, 65 C. 30'	Heated Serum, 70 C. 30'
1.0	0	0	0	Comp.
0.75	0	0	0	Comp.
0.5	0	0	0	Comp.
0.35	0	0	+++	Comp.
0.25	0	0	Comp.	Comp.
0.15	0	++	Comp.	Comp.
0.1	0	Comp.	Comp.	Comp.
0.075	+	Comp.	Comp.	Comp.
0.05	+++	Comp.	Comp.	Comp.
0.035	Comp.	Comp.	Comp.	Comp.

TABLE 7.—THE EFFECT OF HEAT ON THE INHIBITION OF NORMAL GUINEA-PIG SERUM AGAINST PANCREATIC DIGESTION

Results in 24 hours at 38 C. with 1 per cent. pancreatin

Half-Normal Serum, C.e.	Unheated Serum	Heated Serum, 56 C. 30'	Heated Serum, 65 C. 30'
1.0	0	0	+
0.75	0	0	Comp.
0.5	0	0	Comp.
0.35	0	0	Comp.
0.25	0	0	Comp.
0.15	0	0	Comp.
0.1	0	Comp.	Comp.
0.075	0	Comp.	Comp.
0.05	0	Comp.	Comp.
0.035	++++	Comp.	Comp.
0.025	Comp.	Comp.	Comp.

Tables 5, 6 and 7 show that the inhibiting action of normal serum against pancreatin digestion is affected by heating. It was fairly affected by heating for thirty minutes at 56 C., and lost its power at 65 or 70 C., corresponding to the results of Hahn, Cathcart, Rubenstein, Rosenthal and Jobling and Peterson, but not to those of Jochmann-Kantorowicz, Kämmerer, and Kämmerer and Aubry. The extent of the effect of heating, however, differs on the different species of animals, according to the tables; that is, rabbit serum has the weakest resistance against heating compared with ox, sheep, and guinea-pig serum; guinea-pig serum has the strongest resistance to heating; ox and sheep serum are almost equal in this respect and have a stronger resistance than rabbit serum, but weaker than guinea-pig serum. It may be said that the antitryptic substance of normal serum is fairly thermostabile, and also that the quantity of this substance seems to be constant.

C. PRECIPITATION OF NORMAL RABBIT SERUM BY PANCREATIN SOLUTION

According to current literature, we have two views on the essential nature of the antitryptic substance of normal serum, namely, that of a true immune antibody, according to Wiens, Eisner, and Mayer, and of nonspecificity, according to Cathcart, Döblin and Rosenthal. We also have three views of the production of so-called antitrypsin in normal serum. According to Landsteiner the antitryptic action is intimately connected with the albumin fraction, which is approved by Cathcart and Rosenthal. According to Glaessner and Kämmerer

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the antitryptic action is associated with globulins. The third view is that the ferment inhibiting substance of the serum are the lipoids, as advocated by Schwartz, Sugimoto, and Jobling and Peteresen.

The interesting question as to whether or not the antitryptic substance is a true antibody, and what the source of this substance is, invited my further attention. If this antitryptic substance is a true antibody it must have immune reactions, so that I carried out the following experiment for the determination of immune reactions.

EXPERIMENT 3.—Determination of Immune Reactions. For this experiment the serums of forty-one normal rabbits were employed; for the precipitation, trypsin (Central Scientific Co.), pancreatin (Parke, Davis & Co.), and amyllopsin (Digestive Ferments Co.) were used as antigen. The antigens were employed in 1 per cent. solution (dissolved in 0.25 per cent. sodium chlorid solution), filtered through a Berkefeld filter. I obtained four positive results out of a total of forty-one cases, as shown in Table 8.

TABLE 8.—PRECIPITATION OF NORMAL RABBIT SERUM BY TRYPSIN

Dilution of Half-Normal Serum, C.c.	Rabbit A			Rabbit B			Rabbit C			Rabbit D		
	Tryp- sin	Pan- cre- atin	Amy- lop- sin	Tryp- sin	Pan- cre- atin	Amy- lop- sin	Tryp- sin	Pan- cre- atin	Amy- lop- sin	Tryp- sin	Pan- cre- atin	Amy- lop- sin
1.0	+	—	—	+	—	—	++	—	—	+	—	—
0.75	+	—	—	+	—	—	+	—	—	+	—	—
0.5	+	—	—	+	—	—	+	—	—	+	—	—
0.25	±	—	—	—	—	—	±	—	—	±	—	—
0.125	—	—	—	—	—	—	—	—	—	—	—	—

— = negative; + = very slight positive; ± = trace.
41 cases; 37 cases negative; 4 cases positive.

These results show that the anti-enzyme-like substance of normal serum seems to have a special affinity for trypsin, according to Wiener's view, and also the quantity of this so-called antitrypsin is constant.

According to Landsteiner, I treated the four positive serums for fifteen minutes in a half saturation with ammonium sulphate, and tested it again for precipitation. I could not find any precipitation at all. The precipitation of the untreated serum with ammonium sulphate for trypsin should be only a pseudoprecipitation. If, again, the albumin fraction has an important significance in the inhibiting action of serum, the serum of rabbits and guinea-pigs treated with ammonium sulphate might lose the inhibiting action.

With this point in view I examined the serum treated with ammonium sulphate $(\text{NH}_4)_2\text{SO}_4$ for the inhibiting action of pancreatin on fibrin digestion, but could find only a very slight decrease, as shown in Tables 9 and 10.

TABLE 9.—COMPARISON OF THE INHIBITING POWER OF RABBIT SERUM TREATED AND UNTREATED WITH AMMONIUM SULPHATE AGAINST THE FIBRIN DIGESTION OF PANCREATIN

Result in 24 hours at 38 C. with 1 c.c. of 1 per cent. pancreatin

Half-Normal Serum, C.c.	Rabbit A		Rabbit B		Rabbit C		Rabbit D	
	Untreated	Treated	Untreated	Treated	Untreated	Treated	Untreated	Treated
0.5	0	0	0	0	0	0	0	0
0.35	0	+++	0	Comp.	0	+++	0	++++
0.25	++	Comp.	+++	Comp.	++	Comp.	++	Comp.
0.15	++++	Comp.	Comp.	Comp.	+++	Comp.	+++	Comp.
0.1	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.

Control: 1. $(\text{NH}_4)_2\text{SO}_4$ ($\frac{1}{2}$ Sat.) + pancreatin + fibrin = complete digestion.
2. NaOH (0.85 per cent.) + pancreatin + fibrin = complete digestion.

TABLE 10.—COMPARISON OF THE INHIBITING POWER OF GUINEA-PIG SERUM TREATED AND UNTREATED WITH AMMONIUM SULPHATE AGAINST THE FIBRIN DIGESTION OF PANCREATIN

Result in 24 hours at 38 C. with 1 c.c. of 1 per cent. pancreatin

Half-Normal Serum, C.c.	Untreated	Treated
0.15	0	0
0.1	±	Comp.
0.075	++++	Comp.
0.05	Comp.	Comp.

The results in Tables 9 and 10 show that the so-called antitrypsin of normal serum is not a true antibody as Wiens, Eisner and Mayer believed, but acts like a "pseudo-antiferment," or especially like a "pseudo-antitrypsin" in this instance, and the albumin fraction of serum has not an important significance for the antitryptic action as Landsteiner, Cathcart, Döblin and Rosenthal believed, but it seems to have more or less relation to the antitryptic power of the serum.

D. THE RELATION BETWEEN THE ANTITRYPTIC ACTION OF NORMAL SERUM AND ANTICOMPLEMENT

Believing that a factor of the antitryptic action of normal serum would also be associated with complement, I tried to find out the relation of the antitryptic action to the anticomplement. For this experiment I employed the serums of two rabbits and a normal guinea-pig.

First I examined the inhibiting action of the rabbit serum against the fibrin digestion of pancreatin, the precipitation for guinea-pig serum and the complement fixation; after that I immunized the rabbits

TABLE 11.
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TABLE 11.—INHIBITING ACTION OF THE SERUM OF RABBITS A AND B BEFORE AND DURING IMMUNIZATION WITH NORMAL GUINEA-PIG SERUM

Result in 24 hours at 38 C.

Half-Normal Serum, C.e.*	Before Injection		During Immunization	
	Rabbit A	Rabbit B	Rabbit A	Rabbit B
0.5	0	0	0	0
0.35	0	0	+	++
0.25	++	+	Comp.	Comp.
0.15	+++	+++	Comp.	Comp.
0.1	Comp.	Comp.	Comp.	Comp.

* One c.e. of 1 per cent. pancreatin was added to each tube, and a small piece of earmin-stained oxifibrin was used as in the first experiment.

TABLE 12.—PRECIPITATION OF THE SERUM OF RABBITS A AND B BEFORE AND DURING IMMUNIZATION WITH GUINEA-PIG SERUM

Serum, C.e.*	Before Injection		During Immunization	
	Rabbit A	Rabbit B	Rabbit A	Rabbit B
1.0	0	0	++++	+++++
0.5	0	0	+++	++++
0.25	0	0	++	+++
0.1	0	0	+	++
0.05	0	0	+	++
0.025	0	0	+	+
0.01	0	0	0	+
0.005	0	0	0	±

* One c.e. of a 20 times dilution of guinea-pig serum as antigen was used for this examination.

TABLE 13.—COMPLEMENT FIXATION OF THE SERUM OF RABBITS A AND B BEFORE AND DURING IMMUNIZATION WITH NORMAL GUINEA-PIG SERUM

Rabbit Serum, C.e.*	Before Injection		During Immunization	
	Rabbit A	Rabbit B	Rabbit A	Rabbit B
1.0	None	None	Complete	Complete
0.5	None	None	Complete	Complete
0.25	None	None	Almost complete	Complete
0.1	None	None	Partial	Almost complete
0.05	None	None	Trace	Partial
0.025	None	None	None (complete hemolysis)	None (complete hemolysis)

* 1. Rabbit serum was inactivated for thirty minutes at 56 C. 2. Complement employed, 0.5 c.e. of a 10 per cent. guinea-pig serum. 3. Five per cent. sheep blood 0.5 c.c. + 0.2 per cent. antisheep serum, 0.5 c.e.

with normal guinea-pig serum and tested the serum again for the inhibiting action against pancreatic digestion, the precipitation for guinea-pig serum and the complement fixation with the immunized rabbit serum. These experiments are as follows:

EXPERIMENT 3.—Protocols of Experiment 3. Rabbit A: Feb. 8, 1918. Body weight, 2,500 gm. Bled and tested with this serum for precipitation for guinea-pig serum, complement fixation, and inhibiting action against fibrin digestion of pancreatin.

After these examinations I injected 5 c.c. of a 10 times dilution of guinea-pig serum (0.1 c.c. of 10 times dilution of guinea-pig serum hemolyzed completely 0.5 c.c. of 5 per cent. sheep red blood corpuscles suspension).

February 9. Body weight, 2,450 gm. Injected 5 c.c.

February 10. Body weight, 2,420 gm. Injected 5 c.c.

February 11. Body weight, 2,420 gm. Injected 10 c.c.

February 13. Body weight, 2,410 gm. Injected 15 c.c.

February 22. Body weight, 2,600 gm. Bled on the ninth day after the last injection and tested for the precipitation of guinea-pig serum, the complement fixation, and the inhibition against the fibrin digestion of pancreatin.

Rabbit B: Feb. 8, 1918. Body weight, 2,450 gm. This case was treated the same as Rabbit A. Injected 5 c.c. (10 guinea-pig serum).

February 9. Weight, 2,400 gm. Injected 5 c.c.

February 10. Weight, 2,400 gm. Injected 5 c.c.

February 11. Weight, 2,350 gm. Injected 10 c.c.

February 13. Weight, 2,350 gm. Injected 12 c.c.

February 22. Weight, 2,200 gm. Bled the ninth day after the last injection and tested for

The results shown in Tables 11, 12 and 13 indicate that the anti-complement to the complement of guinea-pig serum and the "anti-pseudo-antitrypsin" were surely formed in the immunized rabbit serum, and the antitryptic action of the immunized rabbit serum was decreased.

In 1902, Korschun³⁹ found that antiantilab-ferment was formed in serum by the injection of normal horse serum, which contains an antilab, into normal horse; this observation relates to the chemical reaction. I suppose that the action of the antilab ferment of normal horse serum, decreased by the production of the antiantilab, would also probably be associated with the production of anticomplement, as in my experiments.

E. APPEARANCE OF A TRYPTIC ENZYME IN NORMAL URINE

Enzymes of various kinds have been isolated from normal urine. Among these may be mentioned pepsin (Brücke,⁴⁰ Sahli⁴¹); trypsin (Kühn,⁴⁰ Bendersky,⁴⁰ Tesulli,⁴⁰ Sahli⁴¹); diastatic ferment (Cohn-

39. Korschun: Hoppe-Seyler's Ztschr. f. physiol. Chem., **36**: 1902.

40. Brücke: Kühn, Bendersky, Tasuli, Colinheim, Grützner, Holovtschiner, Helwes, Hopkins, Neumeister and Boas: Huppert-Neubauer, Ed. 10, 1908, p. 599.

41. Sahli: Pflüger's Arch. f. d. ges. Physiol., **36**: 1885.

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heim⁴⁰), and lab ferment (Grützner,⁴⁰ Holovtschiner,⁴⁰ Helwes⁴⁰). Among these proteolytic enzymes in normal urine, Hopkins⁴⁰ could not prove trypsin, Neumeister⁴⁰ pepsin in rabbit urine, and Boas⁴⁰ lab ferment at all; and Matthes,⁴² in 1903, stated that pepsin appears in normal human and dog urine but not trypsin. Schoenborn,⁴³ in 1910, stated that pepsin, diastase and rennin all have been found in normal urine, but trypsin is chiefly a trypsinogen, especially abundant after a meat diet.

EXPERIMENT 4.—*Tryptic Enzyme in Normal Urine.*—I wanted to know whether or not a tryptic ferment appears in normal urine and I experimented with the urine of nine normal rabbits. The colorimetric method for the digestion of the carmin-stained ox fibrin was used and the urine was aseptically taken from the bladder and centrifugalized before the examination.

TABLE 14.—TRYPTIC ACTION OF NORMAL RABBIT URINE
Results in 24 hours at 38 O.

Dilution Used,* C.c.	Rabbit 1	Rabbit 2	Rabbit 3	Rabbit 4	Rabbit 5	Rabbit 6	Rabbit 7	Rabbit 8	Rabbit 9
1.0	0	0	0	Comp.	0	0	Comp.	0	0
0.75	0	0	0	Comp.	0	0	Comp.	0	0
0.5	0	0	0	Comp.	0	0	Comp.	0	0
0.35	0	0	0	Comp.	0	0	++	0	0
0.25	0	0	0	0	0	0	+	0	0
0.15	0	0	0	0	0	0	0	0	0
0.1	0	0	0	0	0	0	0	0	0

* The urine was filtered aseptically through Berkefeld filter. A piece about the size of an apple seed of the carmin-stained ox fibrin was added to each tube containing the urine, the contents covered with toluol and incubated for twenty-four hours.

Table 14 shows that a tryptic enzyme may appear in a small amount in normal rabbit urine in a few cases (two in nine cases).

F. THE APPEARANCE OF ANTITRYPSIN IN NORMAL URINE

Döblin,⁴⁴ in 1909, found antitrypsin in normal urine (positive results in four of thirty cases) with the casein method, but Müller and Kolaczek,⁴⁵ in 1907, could find no antitrypsin in normal urine. In my experiments I could find no antitrypsin in normal rabbit urine; I therefore made the following experiment:

EXPERIMENT 5.—*Determination of Antitrypsin in Normal Rabbit Urine.*—For this experiment I employed the urine of nine normal rabbits obtained from the bladder and centrifugalized before the examination. I used a 1 per cent.

42. Matthews: Arch. f. exper. Path. u. Pharmakol., **49**: 1903.

43. Schoenborn: Ztschr. f. Biol., **53**: 1910.

44. Döblin: Ztschr. f. Immunitätsf. u. exper. Therap. **4**: 1909.

45. Müller and Kolaczek: München. med. Wchnschr., 1907, No. 8.

trypsin (Central Scientific Co.) in salt solution, filtered through a Berkefeld filter, and for the test for inhibiting action to fibrin digestion I used 0.2 c.c. of a 1 per cent. pancreatin (Parke, Davis & Co.) in salt solution, filtered through Berkefeld filter. I could obtain no positive result for the precipitation of the immune reaction, nor any positive reaction for inhibition against pancreatic digestion. (A piece about the size of an apple seed of carmin-stained oxfibrin in 1 c.c. of urine was completely digested with 0.2 c.c. of a 1 per cent. pancreatin.)

G. THE ESSENTIAL NATURE OF THE ANTITRYPTIC ACTION OF NORMAL SERUM

Considering my foregoing experiments, the essential nature of the antitryptic action of normal serum can not be explained in a simple manner, but it is reasonable to suppose that there are existing non-specific "pseudo-antiferments," especially "pseudo-antitrypsin" in this instance. As a product of the physiologic processes of tissue cells these "pseudo-antiferments" not only inhibit the autodigestion of tissue cells, but also foreign ferments outside of the body.

The increase of the antitryptic power of the serum in malignant diseases such as carcinoma and sarcoma, or acute and chronic diseases such as pneumonia, typhoid fever, tuberculosis, syphilis, chronic anemia, etc., can be explained by the increase of "pseudo-antiferments" in order to prevent the autodigestion of tissue cells or foreign ferments. These "pseudo-antiferments," therefore, are of important significance for the antiferment-like action of serum.

The reason for this opinion is that the essential nature of the antitryptic action is a nonspecific "pseudo-antiferment" and that the antitrypsin-like substance of normal serum is fairly thermostabile, and sometimes takes the place of the "pseudoprecipitation" by trypsin; that the production of antipseudo-antitrypsin, as well as the quantity of antitrypsin-like substance, is constant and the normal serum also has the inhibiting action against enzymes of various kinds as observed by many workers.

As the secondary factors, the albumin fraction and the complement of the serum are associated with it, because the antitryptic action is stronger in the serums of animals which have a strong complement, like guinea-pig serum, and also stronger in the serums which have an abundance of serum albumin, such as ox, sheep, and guinea-pig serums, as well as decreased by the production of anticomplement, and also by the treatment of the serum with ammonium sulphate.

H. THE FATE OF THE ENZYME PANCREATIN INTRODUCED INTO THE BLOOD STREAM OF NORMAL RABBITS

1. *The Fixation of Pancreatin Injected as Antigen.*—The statement is often made in regard to the origin of antibodies that antibodies are formed in the blood itself by the leukocytes or the hemopoietic organs.

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Up to a recent time, however, we have no conclusive evidence of that, but Hektoen and Carlson,⁴⁶ in 1909, found that the antigens injected intravenously, at least in some animals, are quickly removed from the blood or in some way so changed that the antigenic property is lost, and antibodies are not produced in the blood. The removal or change of the antigen takes place within three to six hours. Antibodies in active immunization are produced outside of the blood stream. According to Luckhardt and Becht's⁴⁷ observation in 1911, the production of the antibodies with "immune" tissue, specific antibodies with "immune" spleen were obtained, while "immune" heart muscle, liver, bonemarrow and lymph gland did not give positive results. They concluded that the spleen takes a significant part in the fixation of antigen. Luckhardt and Becht, however, found the production of antibody resulted even in asplenic animals. In 1912, Pettit and Carlson⁴⁸ observed that the soluble and insoluble antigens are fixed outside of the blood stream. Recently, Kyes⁴⁹ has shown that certain endothelial cells of the liver and spleen are constantly active in phagocytosing red blood corpuscles from the circulating blood stream; these he designates as "hemophages." This interesting investigation was trustworthily proved by Cary,⁵⁰ Berry and Melick⁵¹ in this laboratory. On the possibility of the activity of these hemophages, Kyes explained that foreign erythrocytes, certain bacteria and some colloids injected into the blood stream are rapidly taken up and digested by the hemophages, so that the hemophages are definitely concerned in antibody production.

Kyes,⁵² by his study, in 1916, on the natural resistance of the pigeon to the pneumococcus, has shown that phagocytosis of fixed tissue cells is not only most active in the hemophages of liver and spleen, but exists in the fixed tissue cells of lung, bonemarrow, kidney, pancreas and intestine, although its activity is very weak. Bartlett and Ozaki,⁵³ in 1917, also stated that *Micrococcus aureus* introduced into the blood stream of dogs is stored up in relatively great numbers in the lung capillaries and is rapidly ingested by morphonuclear leukocytes, but in considerable numbers in wandering cells and fixed cells of the spleen and liver, and also in small numbers, or not at all, in the blood, bonemarrow, kidney, intestinal wall, heart muscle and skeletal muscle. It seems to me that they⁵⁴ are surely proving Kyes' observation by

46. Hektoen and Carlson: Tr. Chicago Path. Soc., 8: 1909, No. 1.

47. Luckhardt and Becht: Tr. Chicago Path. Soc., 8: 1911, No. 6.

48. Pettit and Carlson: J. Infect. Dis., 10: 1912, No. 1.

49. Kyes: Internat. Monatschr. f. Anat. u. Physiol., 31: 1914.

50. Cary: J. Infect. Dis., 17: 1915, No. 2.

51. Berry and Melick: J. Immunol., 1: 1916, No. 1.

52. Kyes: J. Infect. Dis., 18: 1916, No. 3.

53. Bartlett and Ozaki: J. Med. Res., 35: 1917, No. 3.

54. Bartlett and Ozaki: J. Med. Res., 37: 1917, No. 1.

their study on phagocytosis in vivo under various conditions, because the bacteria employed by them were phagocytosed in great numbers by the fixed tissue cells of liver and spleen.

According to Ozaki,⁵⁵ the accumulation of bacteria in the spleen, such as occurs in experimental bacteremia, depends on the vital activity of the cells and the mechanical filtration of bacteria by the spleen, which is not an important factor. The kidney, on the other hand, may be a much more effective filter than the spleen. Recently, Okazaki⁵⁶ found by his study on the fate of the starch granules injected into the rabbit's vein that some colloidal substance such as starch was phagocytosed by some endothelial cells such as those of lung capillaries and Kupffer's cells, or some giant cells.

The following experiments on the fate of the pancreatin introduced into the blood stream of rabbits might explain the significant rôle of the physiologic function of tissue cells against foreign colloids, as well as the fixation of antigens by tissue cells.

EXPERIMENT 6.—Fate of Pancreatin Introduced Into the Blood.—For this experiment I employed fifty-three rabbits, which were injected with pancreatin intravenously. I also used nine other rabbits for control examinations. The experimental rabbits were killed with chloroform at intervals in order to determine the fate of pancreatin injected as antigen; that is, to find out where the antigen was fixed, or if it was fixed, whether or not it had a timely relation.

With this point in view, seven rabbits were killed thirty minutes after the injection, 10 rabbits at one hour, 7 at one and a half hours, 6 at two hours, 3 at two and a half hours, 2 at three hours, 1 at five hours, 1 at six hours, 1 at twelve hours, 3 at twenty-four hours, 2 at thirty-eight hours, 5 at forty-eight hours, 3 at fifty-four hours, 1 at sixty hours, and 1 at seventy-two hours, and also 9 for control.

As an antigen to be injected, 1 per cent. native pancreatin filtered through a Berkefeld filter and 2 per cent. alcoholic pancreatin were used.

Glycerin extracts of the rabbits' organs, such as bone-marrow, spleen, liver, kidney, suprarenal capsule and lung, were made. The examination was then carried out on the following material:

1. Half-normal serum. 2. Ten per cent. organ glycerin extracts. This latter extract was prepared in the following way: The organs were cut into small pieces with scissors and ground up by mixing with sea sand in a mortar and then extracted with 50 per cent. glycerin solution. This extract, after being kept for twenty-four hours at room temperature, was mixed with a small amount of chloroform to avoid putrefaction, following Salkowski's⁵⁷ suggestion. Finally, this extract was filtered through a porcelain filter.

Method of Examination.—The method of carmin-stained fibrin digestion was employed to obtain an indication of the presence of antigen in three tissue extracts and serum. The tissue extracts and serum were examined in graded dilution with a physiologic sodium chlorid solution to the amount of 2 c.c. in every tube, and a small piece of fibrin the size of an apple seed and the solution covered with toluol and then incubated for twenty-four hours at 38 C. To the fibrin digestion of the tissue extract there was added 1 drop of tenth-normal sodium hydroxid to each tube. During this examination aseptic precautions were observed as far as possible.

55. Ozaki: J. Med. Res., 36: 1917, No. 3.

56. Okazaki: The Sei-i-Kwai Med. J. (Tokio), 36: 1917, No. 10.

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By this method the following results were obtained: In 7 rabbits killed thirty minutes after injection the antigen was found in the bonemarrow in 6 cases, in the spleen in 5 cases, in the liver and lung in 2 cases, in the kidney in 1 case and in the suprarenal capsule in 4 cases. In 10 rabbits, killed after one hour, antigen was found in the bonemarrow and liver in 7 cases, in the spleen in 6 cases, in the kidney in 4 cases, in the suprarenal capsule in 5 cases and in the lung tissue in 3 cases; no antigenic reaction was found in 1 of 10 cases. In 7 rabbits, killed after one and a half hours, the antigen was found in the bonemarrow in 5 cases, in the spleen and liver in each of 2 cases, in the kidney in 2 cases, in the suprarenal capsule in 4 cases and in the lung in 1 case. In 6 rabbits, killed after two hours, the antigen was found in the bonemarrow in 4 cases, in the spleen in 3 cases, in the liver in 5 cases, in the kidney and suprarenal capsule in 2 cases, while there was no antigenic reaction in any extract in 1 of 6 cases.

In 3 rabbits, killed at two and a half hours, antigen was found only in the bonemarrow and liver of 1 case each; in 2 rabbits, killed at three hours, in only the bonemarrow, liver and kidney of each case; in 1 rabbit, killed at five hours, antigen was found in the bonemarrow and spleen; in 1 rabbit, killed after six hours, it was found in the bonemarrow, spleen, liver, kidney and suprarenal capsule; in 1 rabbit, killed at twelve hours, it was found in the bonemarrow, spleen, liver and kidneys; in 3 rabbits, killed at twenty-four hours, it was found in the bonemarrow and spleen in each case, in the liver in 1 case, and in the kidney in 2 cases; in 2 rabbits, killed at thirty-eight hours, it was found in the bonemarrow, spleen, kidney and suprarenal capsule of each case, and in the liver in 1 case; in 5 rabbits, killed at forty-eight hours, it was found in the bonemarrow and spleen in each case, and in the liver and kidney in 3 cases; in 3 rabbits, killed at fifty-four hours, 1 rabbit killed at sixty hours, and also 1 at seventy-two hours, no antigenic reaction was found.

Of the antigenic reaction of the serum, it was positive in 6 of 7 animals, which were killed at thirty minutes after injection; in 8 of 10 cases killed at one hour, in 5 of 7 cases killed at one and a half hours, and in 4 of 6 cases killed at two hours, while a negative result was obtained in other cases; also, at the same time, the inhibiting action of the serum against pancreatic digestion was examined in order to determine the presence of the antigen in the serum, concerning which I obtained the following results: the inhibiting action of the serum of rabbits killed within two hours after the injection was markedly decreased compared with that of normal serum, while no decrease of this power was found in cases in which the rabbit was killed after two hours.

As a control, tissue extracts and serum of nine rabbits were carefully examined for pancreatic action, but no positive results were found.

Summarizing these facts, the enzyme, pancreatin, introduced into the blood stream was probably phagocyted by the fixed tissue cells of the body, and seemed to keep its activity during two days, while the antigen in the serum seemed to exist for two hours after the injection, and after that would be phagocyted by fixed tissue cells. The antigen seemed to be markedly phagocyted in the hemopoietic organs within one hour after injection, although it was more or less fixed by other organs.

2. *The Excretion of Pancreatin Injected as Antigen.*—As I have already shown, the urine of some normal rabbits contains a small amount (0.35, or 0.25 in the lowest active dilution) of some tryptic enzyme. In my foregoing experiment it was positive in two of nine rabbits. I carried out the following experiment with a view of finding out whether or not pancreatin introduced into the blood stream is excreted into the urine; if so, how much is excreted.

EXPERIMENT 7.—*Excretion of Pancreatin in Urine.*—For this experiment I employed the urine taken directly from the bladder of fifty rabbits into which I had injected the pancreatin, and also that of nine normal rabbits. This urine was centrifugalized before examination. The method for the pancreatic digestion of the urine was the same as that for serum.

The urines in six of fifty animals injected and seven of the nine normal specimens were negative. The amount of pancreatin excreted in the urine in the remaining forty-four cases is not large as compared with that of normal urine. I assume, therefore, that the pancreatin is phagocyted by the tissue cells. The excreted pancreatin was found in the urine in from thirty minutes to fifty-four hours after the injection.

I. ANTITRYPTIC ACTION OF IMMUNE SERUMS AND TISSUE EXTRACTS WITH PANCREATIC FERMENTS

I wanted to know the relation between the production of antibodies and the antitryptic action of serums and tissue extracts from animals immunized with pancreatic ferments. For this purpose rabbits were immunized to a higher degree with both unmodified and alcohol modified pancreatin, trypsin, and amylopsin, with which I carried out the experiments. The pancreatic ferment solutions employed were made by the following procedure:

a. *Unmodified pancreatic ferment solutions.* Commercial pancreatin (Parke, Davis & Co.), trypsin (Central Scientific Co.) and amylopsin (Digestive Ferments Co.) in powders were added to physiologic sodium chlorid solution in the amount of 1 per cent. by weight. After repeated shaking the solutions were filtered through hard-pressed filters and finally through Berkefeld candles. The resulting filtrate was clear and sterile.

TABLE 15.—THE ANTITRYPTIC ACTION OF TISSUE EXTRACTS OF IMMUNIZED RABBITS. RESULTS IN TWENTY-FOUR HOURS AT 38 C.

Varieties of Immunization	Control.			
	Eight Normal	Pancre-	Amylopsin	Tryp-

TABLE 15.—THE ANTITRYPTIC ACTION OF TISSUE EXTRACTS OF IMMUNIZED RABBITS.

Varieties of Immunization															Tryp- sin
Pancre- atin		Pancre- atin		Pancre- atin		Pancre- atin		Pancre- atin		Amylop- sin		Amylop- sin			
Rabbit	Rabbit	Rabbit	Rabbit	Rabbit	Rabbit	Rabbit	Rabbit	Rabbit	Rabbit	Rabbit	Rabbit	Rabbit	Rabbit	Rabbit	
2	3	4	5	6	8	9	10	11	17	18	20				
10% Tissue Extract, C.c.	+	0	0	0	0	0	0	++	+	+	++	Comp.	Comp.	Comp.	
	Comp.	+	0	0	++	Comp.	0	Comp.	++	++	++	Comp.	Comp.	Comp.	
	Comp.	Comp.	++	0	++	Comp.	0	Comp.	++	++	++	Comp.	Comp.	Comp.	
	Comp.	Comp.	++	Comp.	++	Comp.	++	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	
	Comp.	Comp.	Comp.	Comp.	++	Comp.	++	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	
Bone Marrow	+	0	0	0	0	0	0	Comp.	±	++	++	Comp.	Comp.	Comp.	
	+	0	0	0	0	0	0	Comp.	±	++	++	Comp.	Comp.	Comp.	
	+	0	0	0	0	0	0	Comp.	±	++	++	Comp.	Comp.	Comp.	
	+	0	0	0	0	0	0	Comp.	±	++	++	Comp.	Comp.	Comp.	
	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	
Spleen	+	0	0	0	0	0	0	Comp.	±	++	++	Comp.	Comp.	Comp.	
	+	0	0	0	0	0	0	Comp.	±	++	++	Comp.	Comp.	Comp.	
	+	0	0	0	0	0	0	Comp.	±	++	++	Comp.	Comp.	Comp.	
	+	0	0	0	0	0	0	Comp.	±	++	++	Comp.	Comp.	Comp.	
	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	
Liver	0	0	0	0	0	0	0	++	+	+	0	Comp.	Comp.	Comp.	
	0	0	0	0	0	0	0	++	+	+	0	Comp.	Comp.	Comp.	
	+	0	0	0	0	0	0	++	+	+	+	Comp.	Comp.	Comp.	
	+	0	0	0	0	0	0	++	+	+	+	Comp.	Comp.	Comp.	
	+	0	0	0	0	0	0	++	+	+	+	Comp.	Comp.	Comp.	
Suprarenal Capsule	+	Comp.	++	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	
	Comp.	Comp.	++	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	
	Comp.	Comp.	++	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	
	Comp.	Comp.	++	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	
	Comp.	Comp.	++	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	
Kidney	0	0	0	0	0	0	0	++	+	+	+	Comp.	Comp.	Comp.	
	±	±	0	0	0	0	0	++	+	+	+	Comp.	Comp.	Comp.	
	++	++	0	0	0	0	0	++	+	+	+	Comp.	Comp.	Comp.	
	++	++	0	0	0	0	0	++	+	+	+	Comp.	Comp.	Comp.	
	++	++	0	0	0	0	0	++	+	+	+	Comp.	Comp.	Comp.	

Complete digestion.

pancreatin + fibrin =

of 1 per cent.

NaCl.

Total amount of tissue extract in each tube made, 2 c.c. with 0.85 per cent. NaCl.
Control test for glycerin: 1 c.c. of a 50 per cent. glycerin + 1 c.c. of 0.85 per cent. NaCl + 0.2 c.c. of 1 per cent. pancreatin + fibrin = complete digestion.
Comp. = complete digestion of fibrin; 0 = no digestion of fibrin (complete inhibition).

b. Alcohol modified pancreatic ferment solutions. A 10 per cent. solution of the same ferments was made in physiologic sodium chlorid solution, and after thorough shaking was filtered through hard-pressed paper. To the resulting filtrate was added 20 volumes of absolute alcohol and the mixture allowed to stand thirty minutes, resulting in the formation of a white precipitate. The mixture was then centrifugalized and the sediment rapidly resuspended in an amount of salt solution making the concentration 2 per cent. relative to the amount of pancreatic ferment powders originally employed.

EXPERIMENT 8.—*The Antitryptic Action of Immune Serum.*—I employed the serums of eleven immunized rabbits and eight normal rabbits for this experiment. For the determination of antitryptic action I used the method of fibrin digestion, as explained before, but I employed 0.35 c.c. of 1 per cent. native pancreatin solution filtered through a Berkefeld-filter as antigen in this instance. I obtained the results shown in the chart; that is, the extent of the digestion of fibrin by pancreatin is markedly decreased in the immune serums as compared with the normal serums, although there is not so much difference in the partial digestions. These results indicate that the antitryptic power of serum is increased by immunization by pancreatin and trypsin, but there is no marked increase of this power in immunization by amylopsin.

EXPERIMENT 9.—*The Antitryptic Action of Immune Tissue Extracts.*—I used tissue extracts from twelve immunized rabbits and twelve normal rabbits (glycerin extracts as before) for determining inhibition against fibrin digestion by pancreatin, employing 0.2 c.c. of a 1 per cent. native pancreatin as a digestive agent in this instance.

The results obtained were as shown in Table 15. The tissue extracts of the eight normal rabbits had no inhibiting action against the digestion of fibrin with 0.2 c.c. of 1 per cent. pancreatin, while the tissue extracts of the immunized rabbits showed a marked inhibiting action against pancreatin, especially noticeable in the liver, kidney, spleen and bonemarrow; only a trace of inhibiting action was found with suprarenal capsule of the rabbits immunized with the pancreatin and none with the suprarenal capsule of rabbits immunized with amylopsin.

These results indicated that liver, kidney, spleen and bonemarrow of rabbits immunized with pancreatin and trypsin exhibited antitryptic power, signifying the production of antibodies against the antigen.

J. CHANGES IN QUANTITY OF GLUCOSE IN SERUM AND LIVER AFTER IMMUNIZATION WITH PANCREATIN

In 1916 Schäfer⁵⁸ asserted that when the pancreas is totally removed, grape sugar is no longer stored in the liver. This seemed to me a very interesting fact, because I also found a change in the quantity of grape sugar in serum and of glycogen in the liver in my experiments on immunization by pancreatin. I felt that if animals

57. Salkowski: Deutsch. med. Wchnschr., 1888, No. 16.

58. Schäfer: The Endocrine Organs, 1916, p. 2.

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could be immunized with pancreatin there might be some change in the quantity of grape sugar in the serum, as well as of glycogen in the liver, so that I experimented with nine rabbits to ascertain the point.

EXPERIMENT 10.—*Quantitative Estimation of Glucose in Serum and Liver After Immunization by Pancreatin by Reduction with Fehling's Solution.*—For this experiment I used a 10 per cent. liver extract (with 50 per cent. glycerin) digested for twenty-four hours, and a half-normal serum tested within two hours after bleeding.

For a control I employed liver extract and half-normal serum of five normal rabbits. The results are shown in Table 16.

TABLE 16.—GRAPE SUGAR OF SERUM AND GLYCOGEN OF LIVER IN IMMUNIZED RABBITS

Number of Rabbit	Varieties of Immunization	Reduction of Fehling's Solution (1 C.c.)	
		10% Liver Extract (1 C.c.)	Half Serum (1 C.c.)
2	A. P.	+ (4)*	+
3	A. P.	+ (5)	±
4	A. P.	+ (5)	±
5	A. P.	0	±
6	A. P.	+ (4)	+ (2)
8	A. P.	+	+ (2)
9	N. P.	+ (4)	+ (2)
10	N. P.	+	+ (2)
11	N. P.	+ (5)	+ (3)
17	N. A.	+ (5)	+ (2)
18	A. A.	+ (5)	+ (3)
20	N. T.	+ (5)	+ (3)
5 normal rabbits, control		+ (6)	+ (4)

* The figure in parentheses following the + indicates the degree of reduction: + = slight positive; + (2) = ++, etc.; ± = trace; 0 = negative.

Table 16 shows that the quantity of grape sugar in the serum was markedly decreased in four cases and moderately decreased in five cases. The quantity of glycogen in the liver also was markedly decreased in three cases, moderately in three cases, and very slightly decreased in three cases after immunization with pancreatin. The decrease in the quantity of grape sugar in the serum and of glycogen in the liver is probably due to the fact that the antipancreatin affects the external secretion of the pancreas. In the immunization with amylopsin and trypsin a slight decrease is shown in the quantity of grape sugar in the serum and glycogen in the liver, as compared with the control cases, although only a few cases were tested.

SUMMARY AND CONCLUSIONS

1. Normal rabbit, guinea-pig, sheep and ox serum have an inhibiting action on pancreatic digestion.
2. The extent of the inhibiting action differs in different species of animals, but the quantity of the inhibiting substance is constant in each in relation to the others.
3. One c.c. of rabbit serum neutralizes 0.006 of pancreatin, and 0.1 c.c. of ox and sheep serum neutralizes 0.008 of pancreatin; also 0.1 c.c. of guinea-pig serum neutralizes 0.013 c.c. of pancreatin.
4. The inhibiting action of normal rabbit, guinea-pig, sheep and ox serums against pancreatic digestion is affected by heating; that is, fairly decreased at 56 C., and is lost by heating for thirty minutes at from 56 to 70 C., so that this inhibiting substance is fairly thermostabile.
5. Some normal serums show a precipitation with trypsin, but this phenomenon disappears on treating the serum with ammonium sulphate.
6. The inhibiting action of normal serum is decreased in a slight degree on treating the serum with ammonium sulphate.
7. I conclude from my various experiments that normal serum contains "pseudo-antiferment" (especially "pseudo-antitrypsin" in this instance).
8. The inhibiting activity of the serum also is decreased more or less by the production of anticomplement and antipseudo-antiferment (especially antipseudo-antitrypsin in this instance).
9. A tryptic enzyme appears in small amount in normal rabbit urine.
10. No antitrypsin was found in normal rabbit urine, and no antitryptic action against pancreatic digestion.
11. On the essential nature of the inhibiting power of normal serum against pancreatin, I propose that there exists nonspecific "pseudo-antitrypsin" as the product of physiologic function of tissue cells, so that this "pseudo-antiferment" is of important significance for the antiferment action of serum, and also, as secondary factors, the albumin fraction and the complement of serum are associated with it.
12. Pancreatin introduced into the blood stream of rabbits is fixed by some of the fixed tissue cells, and seems to keep its activity during two days.
13. The possibility of tissue cells phagocytizing pancreatin seems marked in the hemopoietic organs within one hour after injection, although pancreatin is also fixed by other organs.

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14. The antigen (pancreatin) exists in the blood stream for two hours after injection.

15. The antigen (pancreatin) introduced into the blood stream is excreted into the urine in small amount.

16. The antitryptic power of the serum is increased by immunization by pancreatin and trypsin, and also by amylopsin, though in a slight degree.

17. The tissues of rabbits immunized with pancreatin and trypsin have a strong antitryptic power, especially the liver, kidneys, spleen, and bonemarrow; and also in a slight degree after amylopsin.

18. The quantity of grape sugar in the serum, and of glycogen in the liver, is decreased by immunization with pancreatin; and also in a slight degree after trypsin and amylopsin.

I wish to express my sincere thanks to Prof. P. Kyes for his interest and many helpful suggestions.

CHRONIC CAPILLARY CYANOSIS *

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SAN FRANCISCO

Although general clinical conceptions of the mechanism of cyanosis are vague, it has long been recognized that it may be due to four main causes: (1) deficient oxygenation of the blood; (2) obstruction to normal flow in the capillaries; (3) combinations of 1 and 2, and (4) chemical transformation of the hemoglobin.

Demonstration of the mechanism of the form arising in the capillaries, has, so far as we have been able to determine, not been made and it is conceivable that it might prove important from the standpoint of diagnosis in obscure cases. The first question to decide in such a case would be whether the cyanosis could be due to insufficient oxygenation of the blood. In this connection it is well to emphasize, as Hoover¹ has recently done, that cyanosis arising in the thorax is always due to the passage of venous blood to the left heart. In pneumonia the blood cannot be oxygenated because of exudate in the alveoli, in edema of the lungs because of moisture in the form of foam in the alveoli, in congenital heart disease because of an abnormal opening between the venous and arterial sides of the heart, and in advanced emphysema because of a breaking down of the delicate structures which form the oxygenating surface.

Can we measure by any means the respiratory surface and so estimate the diminished oxygenating power of the lung as a whole? Peabody and Wentworth² have determined the vital air in normal individuals arranged in groups according to height. Thus, the average vital capacity of men 6 feet or over was 5,100 c.c., of men from 5 feet 8½ inches to 6 feet was 4,800 c.c., and of men from 5 feet 3 inches to 5 feet 8½ inches was 4,000 c.c. They did not determine the vital air in pneumonia but found that in individuals with large pleural effusions and consequent collapse of the lung the vital capacity varied between 74 and 42 per cent. of the normal. The vital air, then, may serve as a means to determine the functioning area of the lungs

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* From the medical laboratories of the University of California Hospital.

1. Hoover, C. F.: Moisture in the Air Spaces of the Lungs and Oxygen Therapy, J. A. M. A., 71:880, 1918.

2. Peabody, F. W., and Wentworth, J. A.: Clinical Studies of the Respiration. IV. The Vital Capacity of the Lungs and its Relation to Dyspnea, ARCHIVES INT. MED., 20:443, 1917.

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provided the respiratory center is in a condition of normal irritability and acidosis is not present. For a patient with acidosis will be able to hold his breath for a shorter period because of the tendency of a smaller amount of carbon dioxide to turn the hydrogen-ion concentration of his blood toward the acid side and stimulate his respiratory center.

If obstruction to the passage of blood through the capillaries is a cause of cyanosis, what will be the effect on the alkaline reserve in the tissues, on the number and oxygen content of the red cells, on the viscosity of the blood, and the total metabolism? Cannon, Frazer, and Hooper³ have recently pointed out that concentration of blood in the capillaries, acidosis, and low blood pressure are invariable in shock; and it may be inferred that stagnation of the corpuscles is a factor in the development of the acidosis. Bence⁴ has shown that higher carbon dioxide content of the blood increases its viscosity. Van Slyke⁵ has recently published a method which permits of determination of both the oxygen capacity and the oxygen content of venous blood. It is obvious that it is the difference between these two which represents the amount of oxygen used in the capillaries, provided always that the blood is thoroughly oxygenated in the lungs. In a series of eleven normal individuals this oxygen unsaturation,⁶ or oxygen consumption value, averaged 6.04 volumes per cent., the highest being 8.83, and the lowest 3. As the oxygen capacity is fixed by the hemoglobin of the corpuscles it is a reliable index of their hemoglobin content and may be used clinically as such. The hemoglobin as determined by this method varied from 116 to 94.5 per cent. and averaged 105.7 per cent. in the same series of normal subjects. Peabody, Meyer, and DuBois⁷ have studied the total metabolism in cyanotic patients with cardiac decompensation and found it normal.

The recent presence in the medical ward of the University of California Hospital of two patients with chronic cyanosis has offered opportunity for a study of this phenomenon by modern methods.

3. Cannon, W. B.; Fraser, J., and Hooper, A. N.: Some Alterations in Distribution and Character of Blood in Shock and Hemorrhage, *J. A. M. A.*, **70**:526, 1918.

4. Bence, J.: Klinische Untersuchungen über die Viskosität des Blutes. *Ztschr. f. klin. Med.*, **58**:203, 1906.

5. Van Slyke, D. D.: Gasometric Determination of the Oxygen and Hemoglobin of Blood, *J. Biol. Chem.*, **33**:127, 1916.

6. Lundsgaard, C.: Studies of Oxygen in the Venous Blood, *J. Biol. Chem.*, **33**:133.

7. Peabody, F. W.; Meyer, A. L., and DuBois, E. F.: The Basal Metabolism of Patients with Cardiac and Renal Disease, *ARCHIVES INT. MED.*, **17**:981, 1916.

REPORT OF CASES

CASE 1.—T., a Danish machinist, aged 37, entered the hospital Sept. 2, 1918, complaining of shortness of breath. Two years before admission, following an injury with a drill, he developed an infection of his hand which necessitated wide incision and drainage. After recovery he became progressively more short of breath and blue about his face. Examination showed a marked cyanosis of his lips, ears, and cheeks, fairly marked dyspnea on exertion, and dulness to the right and left of his upper sternum which the roentgen ray showed to be due to a persistent thymus. There was a barely audible tricuspid murmur, a moderately enlarged heart, and a slightly enlarged liver that projected 4 cm. below the costal margin. Such signs of decomposition as edema of the extremities and ascites were not present, but the urine contained a trace of albumin. The lungs and mediastinum were clear and the Wassermann reaction negative. While it was felt that the cyanosis was probably due to increased pressure in the great veins brought about by a weakened right heart, the lack of any usual etiology for heart disease, the apparently minimal leak at the tricuspid valve, the total absence of edema, and the presence of the persistent thymus were features which perhaps warranted the search for other possible factors in its causation.

CASE 2.—E., an American traveling salesman, aged 33, entered the hospital Sept. 10, 1918, complaining of shortness of breath and weakness. He had had Neisser infection five or six times. Six years before admission he lost 85 pounds during an attack of typhoid fever, and though he subsequently regained some weight, he lost it again so that his weight was only 135 pounds. He never recovered his strength after this illness and had shortness of breath, palpitation, and increasing cyanosis, especially for the last two years. There was some cough but only after excessive smoking. Examination showed marked grayish pigmentation and diffuse cyanosis, particularly of the face and mucous membranes, clubbed fingers, and a slightly enlarged spleen. There was marked venous pulsation in the neck, and movement of the lung bases behind was slightly restricted, but the chest otherwise expanded well and there were no râles. Roentgen-ray examination showed a small central heart and old root glands with diffuse grayness of both tops probably indicating an old healed tuberculosis. The blood pressure was 110-50, the Wassermann one plus, and the von Pirquet slightly positive. There were a few leukocytes in the urine. This patient had been studied before admission but because of the evidence of old disease of the lungs a diagnosis of polycythemia had been only tentatively made.

The table shows the laboratory data in both cases. Determination of the oxygen capacity, oxygen content and hemoglobin percentage was made by the Van Slyke method⁸ and the colorimetric method of Palmer⁸ was used as a check. The alveolar air was determined with the Fredericia⁹ instrument and the vital air with an ordinary spirometer. Hematocrit readings were made by centrifuging oxalated blood at high speed in graduated 15 c.c. tubes under paraffin oil. Blood viscosity was roughly measured and expressed in multiples of the time required by a given amount of distilled water to drop from a pipet with

8. Palmer, W. W.: Colorimetric Determination of Hemoglobin, *J. Biol. Chem.*, **33**:119.

9. Fredericia, L. S.: Eine klinische Methode zur Bestimmung der Kohlensäurenschwermetallspannung in der Lungenluft, *Berl. klin. Wchnschr.*, **51**:1268, 1914.

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capillary opening. The plasma bicarbonate was determined by the method of Van Slyke.¹⁰

TABLE GIVING LABORATORY DATA OF CASES REPORTED

	Case 1 (T)	Case 2 (E)
Red Blood Corpuscles:		
Capillary	6,600,000	6,100,000
Venous	5,600,000	6,500,000
Hemoglobin:		
Capillary, per cent.	161	166
Venous, per cent.	156	166
Hematocrit (venous blood), per cent.	40.2	45
Viscosity (venous blood)	5.5	6
Plasma bicarbonate, volume per cent.	52.8	55.7
Alveolar air, mm. Hg.	29.9	31.8
Oxygen capacity (venous blood), volume per cent.	29.05	29.5
Oxygen content (venous blood), volume per cent.	6.28	14.6
Oxygen unsaturation, volume per cent.	22.77	14.9
Vital air, per cent. of normal.	75	73

DISCUSSION

It will be seen from a study of the data presented that both subjects had high peripheral red counts, hemoglobin percentages, oxygen unsaturation values, and viscosity, while the vital air, alveolar carbon dioxide and plasma bicarbonate were lowered in each case. Calculation of the color indexes gave figures far above the usual ones and in the presence of normal blood smears this feature cannot be satisfactorily explained. Such high oxygen unsaturation values in the absence of any cause for anoxemia of the blood coming from the pulmonary veins, suggests very strongly that much more oxygen was absorbed from the blood in its passage through the capillaries than normally, and since cyanosis itself is not accompanied by an increase in total metabolism, are proof that the blood was delayed in its passage from the arterial to the venous side.

The question now arises whether the otherwise unexplained acidosis found in both these subjects was due to this delay as Cannon supposes that it is in shock. Oxidation must be going on in the tissues at a normal rate but the carrying away of intermediary acid metabolites may be so delayed that the alkaline reserve is lowered, and it seems probable that in the absence of other sufficient causes the acidosis may be explained on this basis. Diminution in the vital air must be considered as due to the demonstrated slight acidosis and not to any decrease of the respiratory surface.

The normal venous count in T. shows that the blood was concentrated in the capillaries, and this constitutes the one essential difference

10. Van Slyke, D. D., and Cullen, G. E.: The Bicarbonate Concentration of the Blood Plasma, Its Significance and Its Determination as a Measure of Acidosis, *J. Biol. Chem.*, **30**:289.

in the laboratory findings of the two cases. The significance of this concentration is not evident unless we assume that it was caused by dilation of the capillaries from back pressure.

It is obvious, then, that a solution of the clinical difficulties cannot be obtained from the laboratory data. There is scarcely any doubt as to the sufficient oxygenation of the blood in both cases, but we cannot say definitely that in E. there was not an increase in venous pressure, though the clinical evidence was against it. The high venous count here assumes possible importance as indicating a primary increase in the number of the red corpuscles and viscosity of the blood as a cause of the cyanosis. In the case of T. the slight tricuspid leak and enlarged heart make increased venous pressure most probable, but why this was not accompanied by edema is not clear.

In conclusion, the following tentative explanation of the mechanism of the form of cyanosis under discussion is given:

Cyanosis arises in the capillaries from increased oxygen unsaturation of the blood secondary to its delay in passage from the arterial to the venous side. This delay may be due to increased venous pressure or a primary increase in the red blood cells and viscosity of the blood. It lowers the alkaline reserve by increasing the concentration of acid metabolites in the tissues and thus diminishes the carbon dioxide carrying power of the blood, the alveolar carbon dioxide and the vital air.

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A REPORT ON GOITER AMONG DRAFT MEN FROM THE NORTHWEST*

FRANK P. BRENDDEL AND H. M. HELM

Captain, M. C.

First Lieutenant, M. C.

FORT MCDOWELL, CALIF.

During the May and June examinations of western drafted men at this depot, a remarkable number of thyroid enlargements were noted. Many were unassociated with toxic symptoms, and at first no exact record was made beyond a simple notation of the condition. It soon became evident, however, that a considerable proportion of the cases had true hyperthyroidism and were unfit for general military service. These men were studied with especial reference to nervous and vasomotor instability and cardiac and renal function, and the results tabulated.

Below are noted the quotas from the several states with number of goiter rejections opposite:

State	Quota	Rejected for Goiter
Oregon	2,850	23
Montana	354	5
California	4,550	4
Nevada	49	3
Utah	168	1
Idaho	165	1
New Mexico	405	0
Arizona	318	0
Wyoming	92	0
Total number examined.....	8,951	
Total number rejected.....		37

Evidently there are "goiter areas" in certain of the Northwestern States, notably Oregon and Montana. The high percentage in the Nevada contingent scarcely can be considered because of the small number of men examined.

The detailed findings in thirty-four cases are recorded in Table 1. Of this number, six had very large goiters; twelve had moderate and thirteen slight enlargements. All the Montana cases had marked enlargement; three were very large and would interfere with wearing of uniform and pack. One was causing pressure symptoms, manifested by chronic hoarseness and periods of suffocation. One had been operated on in July, 1917, and had recurred. Twenty had notable

* Submitted for publication Nov. 2, 1918.

TABLE 1.—DATA OF FIRST CONTINGENT*

Case Number	Family History	Locality from Which Sent		Description of Thyroid	Tremor of Hands	Eye Findings				Heart Findings				Blood Pressure		Urinalysis		
		City	State			Stellwag's Sign	Von Graefe's Sign	Moeblus' Sign	Exophthalmos	Tachycardia	At Rest	Immediately after 100	Two Min. After	Systolic	Diastolic	Albumin	Hyalin Casts	Granular Casts
1	—	Ketchikan.....	Alaska	Mod.	—	—	—	—	—	Mod.	96	120	100	160	115	Trace	—	—
2	—	Hanford.....	Calif.	Mod.	Mod.	+	+	—	—	Mod.	+	+						
3	—	Oakland.....	Calif.	Mod.	Mod.	+	+	—	—	Marked	+	+						
4	—	San Francisco..	Calif.	Mod.	Mod.	—	—	—	—	Marked	128	170	140	165	100	Trace	+	+
5	Mother and sister	Yreka.....	Calif.	Slight	Mod.	—	—	—	+	Mod.	88	120	90	+				
6	—	Oakland.....	Calif.	Mod.	Slight	—	—	—	—	Mod.	96	138	112	155	90	Trace	+	+
7	—	Unknown.....	Mod.	—	—	—	—	—	Mod.	108	128	114	150	100	Trace	+	+
8	—	San Jose.....	Calif.	Slight	Slight	—	+	—	—	Marked	+							
9	—	Blackfoot.....	Idaho	Slight	—	—	+	+	+	+								
10	—	Niely.....	Utah	Slight	Slight	+	+	+	+	—	84	102	78	140	70	Trace	+	+
11	—	Carson City....	Nev.	Marked	—	—	—	—	—	Mod.	108	126	114	150	95	Trace	+	+
12	—	Reno.....	Nev.	Marked	Slight	+	+	+	+	—								
13	—	Reno.....	Nev.	Mod.	—	—	—	—	—	—	70	78	72	162	100	+	+	+
14	—	Hamilton.....	Mont.	Mod.	Slight	+	+	+	—	Slight	+							
15†	—	Forsyth.....	Mont.	Marked	—	—	—	—	—									
16§	—	Forsyth.....	Mont.	Marked	—	—	—	—	—									

* This table consists of cases rejected on the first contingent received. We had but one blood pressure instrument, a Tycoos, which was continually breaking or out of order. Our records were not as complete in detail as the later series. The later series are accurate results. The blood pressure having been taken by Merer instrument, mercury type, thus eliminating errors due to spring and all results were carefully recorded.

17	Livingston.....	Mont.	Marked	—	—	—	—	—	—	76	120	120	84	—	—	Heavy	Marked
18	Baker.....	Ore.	Mod.	—	—	—	—	—	—	120	160	120	120	80	116	+	Heavy
19	Coquilla.....	Ore.	Slight	Slight	—	—	—	—	—	90	140	96	120	—	—	Heavy	Heavy
20	Eugene.....	Ore.	Mod.	Slight	—	—	—	—	—	104	144	120	120	—	—	Heavy	Heavy
21	Eugene.....	Ore.	Mod.	Marked	—	—	—	—	—	96	135	102	120	90	150	+	Heavy
22	La Grande.....	Ore.	Slight	—	—	—	—	—	—	118	140	120	120	—	—	Heavy	Heavy
23	Minneville.....	Ore.	Mod.	—	—	—	—	—	—	102	180	130	130	90	160	+	+
24	Pendleton.....	Ore.	Mod.	Slight	—	—	—	—	—	120	144	120	120	95	150	+	+
25	Pendleton.....	Ore.	Marked	Mod.	—	—	—	—	—	104	128	108	108	90	160	+	+
26	Portland.....	Ore.	Slight	—	—	—	—	—	—	94	144	100	100	70	140	—	—
27	Portland.....	Ore.	Slight	—	—	—	—	—	—	104	120	124	124	—	—	+	—
28	Portland.....	Ore.	Mod.	Slight	—	—	—	—	—	120	150	100	100	90	145	Trace	—
29	Portland.....	Ore.	Mod.	—	—	—	—	—	—	90	144	114	114	—	—	—	—
30	Portland.....	Ore.	Slight	Slight	—	—	—	—	—	128	136	125	125	80	125	—	—
31#	Portland.....	Ore.	Slight	—	—	—	—	—	—	120	136	120	120	80	135	—	—
32	Portland.....	Ore.	Slight	Slight	—	—	—	—	—	120	158	120	120	—	—	—	—
33	Portland.....	Ore.	Slight	Slight	—	—	—	—	—	96	135	108	108	—	—	—	—
34	Taeoma.....	Wash.	Slight	—	—	—	—	—	—	—	—	—	—	—	—	—	—

† Not recorded.
 ‡ Size interfering with uniform wearing.
 § Causes pressure symptoms and interferes with uniform wearing.
 ¶ Interferes with uniform.
 # Rejected for other causes.

fine tremor; ten had ocular symptoms, and all but five had tachycardia—that is, pulse of 90 or above at rest. There were eight with a standing pulse rate of over 100, and twelve with a rate of 115 or over. Leaving out of consideration the five cases without tachycardia, eight had a pulse count of from 120 to 140 after the standard hopping test (fifty hops on each foot); eight had a count of from 140 to 180, and all were dyspneic. In but three did the rate, two minutes after exercise, return to the original rate. Of eighteen blood pressure estimations, eleven were 150 or above and only three were below 140. Nearly all men showed a trace of albumin in the urine, and several had a definite nephritis.

In July, two contingents of 1,350 men each were received, chiefly from Oregon and California. Of the first 1,250 men from Oregon, 151 had sufficient thyroid enlargement to justify notation to that effect. Sixty cases were tabulated (Table 2).

The question of family history was discussed carefully with forty-eight men, twenty-one of whom gave a positive history and twenty-seven a negative. In fifteen instances female relatives were affected, in three, male, and in three both male and female.

The personal history was variable. Most of the men were farmers or woodsmen, and the great majority were of good physique. Some were not aware of any abnormality whatever; others had noticed a slight fulness of the neck or recalled, when questioned, that they wore a larger collar than formerly, but had no subjective symptoms. Others complained of "nervousness," palpitation and periods of suffocation. Some admitted excitability, quick temper, and fatigue on moderate exertion. Excessive perspiring and diarrhea were mentioned in a few instances. Loss of weight was common and, in several cases, marked. In practically every instance the foregoing symptoms, with the exception of palpitation, were elicited only after persistent cross examination. Almost never did the patient consider that his goiter had any bearing on his condition. The palpitation he attributed to too many cigarettes or late hours.

Six of the goiters were large, twenty-two moderate, and thirty-two small.

Tremor of the hands was almost always present, though at times slight, and somewhat coarse. Like the palpitation it was attributed to cigarettes in many cases.

Marked eye signs were uncommon. Only five men showed distinct exophthalmos, although almost all had a slight widening of the palpebral fissures. Poor convergence was relatively frequent.

Tachycardia was the rule; thirty-six cases having a standing rate of over 90, and twenty-eight of over 100. In over half the cases the

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response to exercise was poor. Hypertension was present in a variable degree; thirty-three cases had a systolic pressure of over 140. In four cases a second reading, taken one or two days after the first, was notably lower than the original reading. This accords with a vasomotor instability that reasonably may be considered toxic although no organic arterial change has occurred.

Albuminuria was noted in but two cases, and considered as a whole, there were fewer severely toxic cases than in the earlier group. Possibly this was due to more strict elimination by local draft boards. The relative toxicity among the two groups, as indicated by the percentage showing the various specific symptoms is given below:

	May and June Group, Per Cent.	July Group, Per Cent.
Tremor	66	61
Tachycardia:		
Pulse 90 to 100.....	83	18½
Pulse over 100.....	66	46
Poor recovery after exercise.....	90	33
Blood Pressure over 140.....	83	55
Albuminuria	83	3½

The subsequent history of the men with palpable thyroids or non-toxic goiters who were enlisted is an interesting speculation. It may be that the change in location and mode of life will cause the gland to resume normal proportions. On the other hand, it seems more likely that the stress and nervous tension incident to army life will greatly aggravate the potential nervous and vasomotor instability and eventuate in a speedy break-down.

CONCLUSIONS

1. Goiter is more common in young men than the experience of the general practitioner would suggest.
2. There are definite goiter districts in Oregon and Montana and probably in Nevada.
3. Locality appears to be much greater in importance than family tendency.
4. Many of the goiters in draft men are unmistakably toxic and should be cause for rejection.
5. The more toxic cases show a tendency to nephritis, in addition to the classical cardiac symptoms.
6. All men having thyroid enlargement should be examined systematically for evidence of cardiorenal pathology.

TABLE 2.—DATA OF LATER CONTINGENTS—(Continued)

Case Number	Family History	Locality from Which Sent		Description of Thyroid	Tremor of Hands	Eye Findings				Heart Findings				Blood Pressure		Urinalysis			Disposition*
		City	State			Stellwag's Sign	Von Graefe's Sign	Moe's Sign	Exophthalmos	Tachycardia	At Rest	Immediately after 100	Two Min. After	Systolic	Diastolic	Albumin	Hyaline Casts	Granular Casts	
48	Sister and brother	Portland.....	Ore.	Mod.	—	+	—	—	—	Mod.	105	141	111	140	87	—	—	—	R
49	Sister	Portland.....	Ore.	Marked	Slight	+	—	—	—	Slight	96	135	102	148	75	—	—	—	R
50	—	Portland.....	Ore.	Palpable	Fine	—	—	+	—	Mod.	108	144	112	150	88	—	—	—	R
51	Father, brother and sister	Portland.....	Ore.	Slight	Slight	—	—	—	—	Mod.	104	132	116	94	56	—	—	—	R
52	—	Portland.....	Ore.	Palpable	—	+	—	—	—	Mod.	108	120	108	150	94	—	+	+	R
53	Paternal aunt	Portland.....	Ore.	Mod.	—	+	+	+	—	—	84	120	93	140	86	—	—	—	R
54	—	Portland.....	Ore.	Mod.	—	—	—	—	—	—	60	75	48	125	85	—	—	—	E
55	—	Portland.....	Ore.	Slight	—	+	+	+	—	Mod.	108	135	99	112	75	—	—	—	R
56	—	Portland.....	Ore.	Mod.	Mod.	+	+	—	—	Slight	98	114	96	134	80	—	+	+	R
57	—	Portland.....	Ore.	Mod.	Mod.	+	—	—	+	Slight	90	141	117	168	93	+	—	—	R
58	Brother	Portland.....	Ore.	Mod.	Mod.	—	—	—	—	—	81	126	93	158	85	—	+	+	R
59	—	Portland.....	Ore.	Mod.	Slight	—	—	+	—	Mod.	108	130	112	138	78	—	—	—	E
60	Mother	Hanford.....	Calif.	Mod.	Marked	—	—	—	+	Mod.	102	132	114	130	80	+	+	+	R
61	—	Alhambra.....	Calif.	Slight	Slight	—	+	—	—	Mod.	104	138	104	125	80	—	—	—	E
62	—	Pasadena.....	Calif.	Mod.	Slight	+	—	—	+	—	88	114	86	140	82	—	—	—	E
63	—	Los Angeles....	Calif.	Slight	Slight	+	—	—	—	Mod.	104	140	104	128	76	—	—	—	E
64	—	McMinnville....	Ore.	Mod.	Mod.	+	—	+	—	—	84	120	90	140	90	—	Few	Few	E

* R = rejected for military service.
E = enlisted for military service.

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NONSPECIFIC THERAPY IN ARTHRITIS AND INFECTIONS

A STUDY OF THE CHANGES IN THE BLOOD CONSEQUENT ON THE INTRA-
VENOUS INJECTION OF TYPHOID PROTEIN

A CONSIDERATION OF THE ANALOGY BETWEEN THE TYPHOID PAROXYSM
AND THE MALARIAL PAROXYSM *

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Many of the clinical effects of the intravenous injection of foreign protein have been known for some time, particularly since the introduction of intravenous dosage of diphtheria antitoxin in diphtheria.¹ It has been observed that, following a previous almost afebrile or slightly febrile period in the course of disease, a more or less pyrogenic reaction followed the intravenous injection of antitoxin. For example, of twenty-six recent cases from my records in the contagious hospital, treated by intravenous injection of antitoxin, twenty-one reacted with chill and rise of temperature. In some cases the rise in temperature was as high as 108 F.

The explanation of this reaction was not generally known until the researches of Vaughan and his co-workers were made (1909). Prior to this time, Buchner (1890), Krehl and Matthes (1895) had induced fever in animals by the subcutaneous injection of bacterial and other proteins.

No importance was attached to the protein reaction as a therapeutic measure until quite recently. Indeed, as yet no cognizance has been given to the possible effect of the foreign protein on the disease process

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* From the Department of Pediatrics and Contagious Diseases, University of Michigan Hospital, and the Cowie Hospital. Address before the Chicago Pediatric Society, May 21, 1918.

1. An Italian physician, Zamboni (Gazz. d. osp., 1900, 8, 4), was the first to use antitoxin by the intravenous route. He reported increase of temperature following the injection. Von Behring (1901) (quoted from Beyer, München. med. Wchnschr., Aug. 26, 1913) recommended the intravenous injection in severe cases of diphtheria. Fette (Med. Klin., 1909, No. 50) reported 145 cases treated by intravenous injections of antitoxin, and he also records temperature reactions. Park (Boston M. and S. J., 168:73, 1913) reported 200 cases, the first in America, treated by this method. He records chill, nausea, vomiting, fever, sweating and pain as common symptoms following the injection.

itself in diphtheria. Efforts have always been directed at minimizing the effect of the protein contained in the antitoxin.

The recent work on the remarkable effects of intravenous injections of foreign protein in arthritis by Miller and Lusk² and others has stimulated not only the usual therapeutic enthusiasm consequent on such reports, but also an interest in studies which may, in the first place, reveal what happens in the body after the foreign protein enters the blood stream; secondly, why these changes bring about an amelioration of symptoms and arrest disease processes; and thirdly, what its effect on the body tissues either for weal or woe may be.

Thus far it has been determined repeatedly that a typical protein reaction is characterized by chilliness or a definite chill, fever, pain, sweating, and characteristic changes in the formed elements of the blood, a leukopenia, followed by a leukocytosis sometimes of very marked degree.³

In 1912 Brown and Ross⁴ reported that there was always a leukocytosis four to ten hours after an intramuscular injection of sodium nucleinate. The count went as high as 23,000 and returned to normal in from three to five days. This calls to memory the early work done in the University of Michigan on leukocytosis induced by the subcutaneous injection of nuclein (Vaughan, 1892). The explanation for this reaction is now elucidated.

We became interested in the changes in the formed elements of the blood. Unable to find any work on the successive cell changes, we directed our attention to this somewhat arduous task, with prospective reward, however, because either positive or negative results seemed to us to be of value. Through the courtesy of Dr. Newburg of the Department of Internal Medicine all adult cases of "arthritis" which did not clear up after the removal of all known foci of infection were referred to us for treatment. These together with three private cases make up our small list of ten carefully studied cases.

The first intravenous injections of typhoid protein (vaccine) we find are those reported by Ichikawa⁵ in Japan. He records eighty-seven cases of typhoid fever treated in this way. An immediate rise in temperature and the end of the disease by crisis occurred in many of the cases.

2. Miller and Lusk: J. A. M. A., 68:764 and 1940, 1917. Boston M. & S. J., January, 1913.

3. Ewing's observations, 1895, are of interest in this connection (New York M. J., 62:196, 1895).

4. Brown & Ross: J. Ment. Sc., 58: 1912.

5. Ichikawa: Ztschr. f. Immunitätsf., 23:32, 1914; abstr. in J. A. M. A., 64: 546, 1915.

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ORDER OF OUR INVESTIGATION

Controls.—In each case a control count preceded the injection or was made at the time of the injection. In a few a prolonged hourly or two hourly control count was made the day preceding the injection. For lack of time and assistance this could not be done in all cases. In Case 10 all the counts were made on 500 cells. In Case 8 most of the counts were on 500 cells. In all others 200 cells were counted. A $\frac{1}{12}$ Leitz oil immersion lens was used in all counts. The leukocyte counts were always made in each case by the same person and were carefully checked. All differential counts were made by us and all abnormal and atypical cells were checked by both of us.

Total leukocyte counts and complete differentials were made starting from the beginning of injection, $\frac{1}{2}$, 1, $1\frac{1}{2}$, 2, 3, 4 and every hour thereafter until the height of the reaction or its end was reached in most cases. Great care was taken to observe closely in controls as well as subsequent counts the presence and the number of abnormal or atypical cells both in the white and the red groups.

A few observations were made on the platelets and also a few spectroscopic observations.

Parke, Davis and Company's typhoid vaccine was used. Two minutes were consumed each time in making the injection, which was always given at least six hours after a meal.

The roentgenographic records are from Professor Van Zwaluwenburg's reports excepting Case 1.

The ten cases were made up as follows:

- 2 chronic multiple peri-arthritis deformans
- 1 hypertrophic arthritis deformans
- 1 chronic multiple peri-arthritis deformans in a child with developmental epiphyseal changes
- 2 "acute rheumatism," polymuscular and periarticular
- 1 atrophic arthritis
- 1 hypertrophic spinal arthritis
- 1 gonorrheal vulvovaginitis
- 1 suppurative mastoiditis with chronic pulmonary tuberculosis

Four of these were children and six were adults.

REPORT OF CASES

CASE 1.—*Polyperi-arthritis deformans, chronic.*

History.—Florence S., aged $11\frac{1}{2}$, entered the Cowie Hospital Sept. 16, 1917, complaining of stiffness and contractures of the legs and upper extremities, cramps in the hips, fever and inability to walk.

Feb. 16, 1911, the patient had measles. The eruption did not "come out good." She had night sweats, was nauseated and had projectile vomiting until May. She was able to be up in July, when it was noticed that she dragged her right foot and leg. She had a severe cough following the measles. In August her head was drawn to one side for a period of three weeks and the arms were drawn up. In September it became impossible for her to walk and contractures began to develop. In October she had an attack of fever (recurrent attacks); her temperature went as high as 103 F., but she had no chills. In January, 1912, she came to the Pediatric Clinic. She was treated by Biers' hyperemic stasis. She began to walk in May, 1912, but it was fall before she walked well. In April, 1915, she had another attack of fever with "inflammatory rheumatism, neuritis and malnutrition" which lasted until September. At this time she walked stiffly, but was able to go seven blocks. The improvement continued until July, 1916, when she had another attack of measles. In November, 1916, she had a chill, temperature 105 F.; was nauseated and had projectile vomiting. Dec. 18, 1916, she had chills and fever, and since then

she had been unable to walk. During this month she had her tonsils and adenoids removed and was treated with an autogenous vaccine made from cultures from the tonsils, without improvement. During December and January she was given passive movements and hot baths. In December, 1917, she walked a few steps across the room. In May she was given stock vaccine without results.

She has always been constipated. In 1914 she had a skin eruption starting as tiny vesicles between the fingers. She now had scaling on the hands, and vesicles about the anus and on the inside of the thigh. The heart was negative.

Blood: Red cells, 4,600,000; whites, 7,200; polynuclears, 54 per cent.; small lymphocytes, 31 per cent.; large lymphocytes, 13 per cent.; transitionals, 2 per cent.

Urine, negative.

Roentgenographic (from Dr. A. W. Crane) report: "Sinuses all negative. Teeth negative. Abnormally dense areas about the hilum of each lung of tuberculous type, but may result from other kinds of infection. Spleen and liver slightly enlarged. Barium gastro-intestinal study negative. Hand, wrist and knee show a decalcifying process in the joint region; joint surfaces, however, are left emphasized, giving the appearance of egg shell fragility, especially the knee joint. The articulating surfaces are smooth. No erosions."

Nonspecific Protein Therapy Record.—This patient was given three injections (Fig. 1) of typhoid vaccine, to each of which she responded with chill, nausea, vomiting, temperature and leukocytic changes associated with pain localized in the back, arms, and legs. Following the second injection the fingers of the left hand became more flexible and it was now possible to insert two fingers between her fingers and palm; this had been impossible before. Following the third injection the patient felt like walking, and with assistance walked down the hall. This was the first time she had walked at all since the previous March (eight months). This day her knees were definitely more flexible than on her entrance and she could flex the toes.

CASE 2.—Chronic periarthritis; no structural joint change.

History.—Mrs. W., aged 59, entered the medical clinic, University Hospital, complaining of pain in the knees, inability to stand or walk, inability to freely move right elbow. Referred to us for treatment March 19, 1918.

Present illness began one year before admission with migrating swelling of the fingers, elbows and shoulders. Three months later the knees became involved, swollen and tender. The fingers and shoulders were better, the right elbow and knees were still involved, the third left finger had one thickened joint. She was unable to stand or walk. The patient had a course of serum treatment, but no chills, fever or pain resulted.

Aside from marked wasting of the musculature of the extremities, contracture of right elbow and knees, marked swelling of the knees (periarticular—no floating of patella), examination was negative. The heart had soft blowing systolic murmur at apex, without enlargement or displacement.

Infected teeth and tonsils had been removed.

Roentgen Report.—The skull showed extensive atrophic changes and therefore was more than ordinarily difficult to read. The frontals were voluminous and air-containing; the ethmoids were very narrow and difficult to see, probably denser than normal, but judgment was difficult because of the bilateral involvement. The antra were small, thin walled and apparently normal. The nasal passages were unusually wide; probably an atrophic rhinitis. The sphenoid was very small, and was scarcely to be distinguished in the density of this region. Diagnosis: Bilateral posterior ethmoiditis. No roentgenogram of joints made.

The patient made no improvement and was referred to us for nonspecific protein treatment.

Nonspecific Protein Therapy Record.—This patient received ten intravenous injections of typhoid vaccine, dosage 1 billion (Fig. 2). Following the first,

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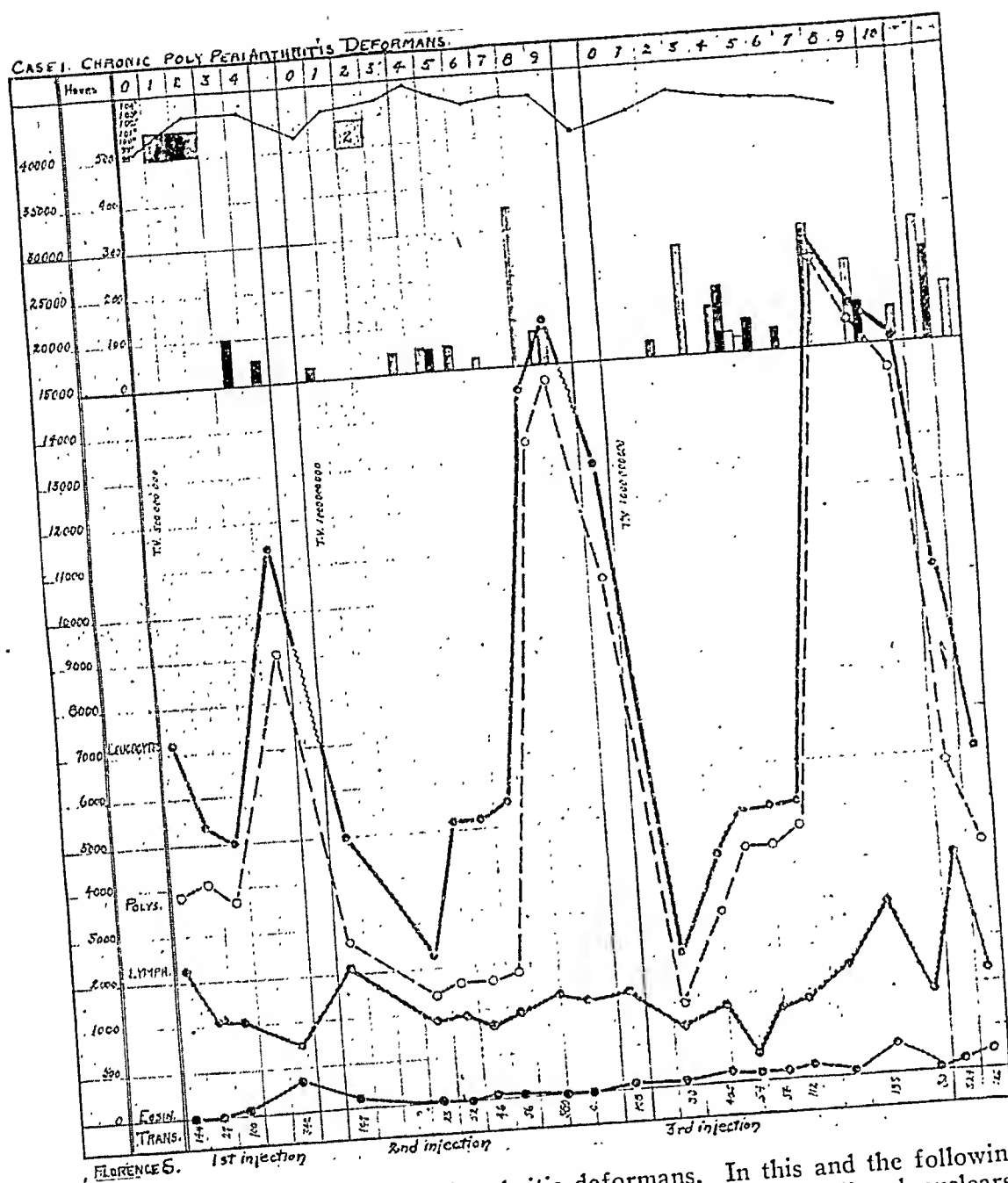


Fig. 1.—Case 1. Chronic polyarthritides deformans. In this and the following charts black columns = myelocytes; white columns = basophil polynuclears; gray columns = atypical cells; squares at top = nucleated reds. The absolute count for blood cells is given in the column at the left. The abnormal cells are drawn on a base line in the upper half of the chart, the absolute count being given in the second column of figures to the left. The black columns represent myelocytes, the white basophilic polynuclears, and the gray the number of atypical cells. The shaded blocks between five thousand and ten thousand represent the normal limits for the total leukocyte count during each reaction. Nucleated red blood corpuscles are indicated by squares at the top of the chart, the figure indicating the number seen during the differential count. The transitionals per cubic millimeter are given in figures at the bottom of the chart. The temperature curve is indicated at the top of the chart.

which caused a slight clinical reaction, her right arm was more stiff than before. After the sixth injection the patient said that for the first time she was able to straighten out her legs and she thought the treatments were benefiting her, but she complained of swelling of the ankles. The chill in the first six reactions was present, but was slight. Following the seventh reaction her knees were swollen, but she could bend and move them without pain and she was very

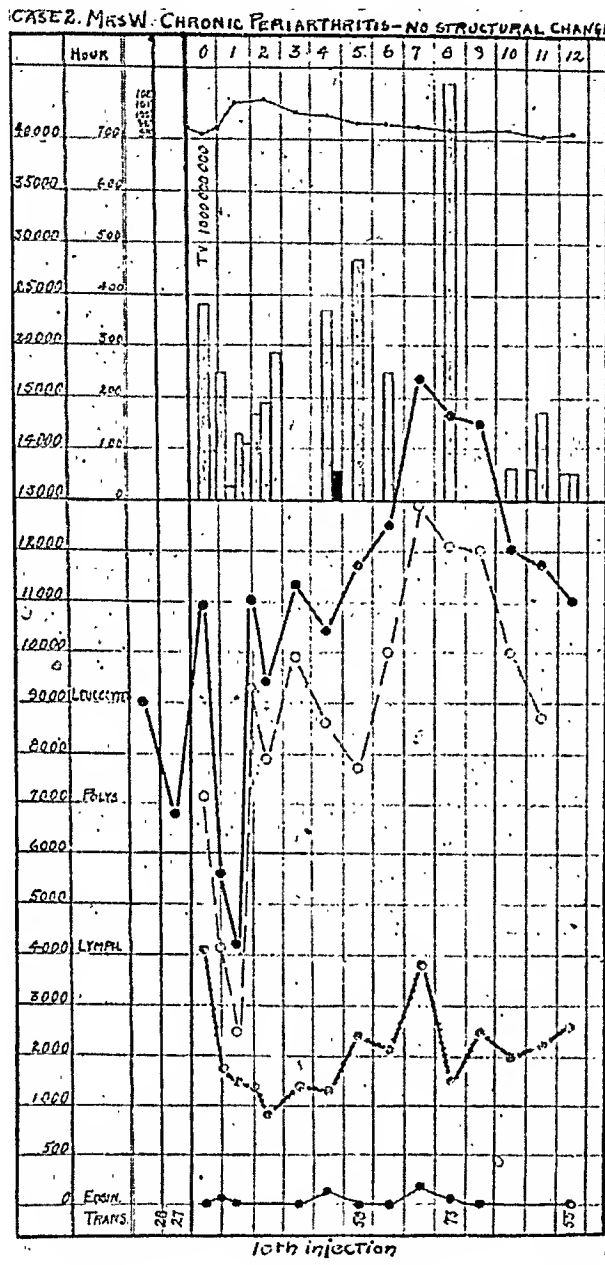


Fig. 2.—Case 2, Mrs. W. Chronic periarthrititis. No structural change.

anxious to attempt to walk. Following the eighth injection she was allowed to walk and took about ten steps. The tenth reaction is recorded on the chart (Fig. 2). She was at the time of the report able to get about by hanging on to the bed and chairs. She stood straighter than previously and showed considerable improvement. The injections were made on the following dates: March 20, 24, 27, and 31; April 3, 6, 11, 13, 16 and 20. Each injection showed the characteristic reaction.

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CASE 3.—*Polyperiartthritis deformans, chronic, infectious.*

History.—Blais, farmer, aged 59, entered the medical clinic Jan. 10, 1918, complaining of pain and swelling and stiffness of many joints, and muscle pain.

The family history was negative.

The present illness began about sixteen years prior to admission with pains in the back, chiefly during the winter months. Three or four days' rest in bed served to clear up the attacks. These attacks occurred frequently until six years prior to admission when they became more severe, and his "hands swelled." He was given intramuscular injections every day for four or five weeks with no benefit. He then took a series of hot baths in conjunction with subcutaneous injections for three weeks; no improvement. After this he took a course of subcutaneous injections of "rheumatic serum" which gave him much relief. At the end of the first week he was markedly improved and was able to return to work. He continued to work until last November, but at no time did the symptoms completely disappear. He was well enough so that he could work; much of the time there was considerable pain in his joints and muscles. This had recently become worse.

Physical Examination.—Large frame; well nourished; large musculature; no teeth; tonsils infected; patient almost entirely helpless; has to be helped from chair to bed; could not remove his shirt or raise his arms above his shoulders; limitation of neck movement. Joints showed marked deformity of metacarpal-phalangeal joint; fingers held in part flexion and stiff; complete extension could be obtained with only a little pain; marked deformity of fingers of both hands and of the left thumb; elbows cannot be completely extended; rotation of shoulder joints markedly limited; knees held in partial flexion; cannot be extended. Some ankylosis of the hips; the pelvis tilts when the leg is raised; the involvement of the joints, for the most part, is periarticular. The roentgenogram showed that the bones themselves are but slightly involved.

The lungs, heart and abdomen are negative.

The tonsils were removed, as they contained large and small pus pockets. The patient was given a course of large doses of acetyl salicylic acid without noteworthy result.

Wassermann negative. Urine negative.

Blood count: Reds, 5,100,000; whites, 8,200; hemoglobin, 70 per cent.

Roentgen Report.—(Dr. Van Zwaluwenburg.) Dorsopalmar stereogram of hands shows extensive deformity, with comparatively little destruction of the bones. Certain of the articulations show an inconsiderable reduction in the joint spaces, and there is some irregularity of the heads and bases of the phalanges. The most typical feature is the subluxation. The lesions are faintly more active in the soft tissues than in the joint itself; jaws negative. Diagnosis, infectious arthritis.

Nonspecific Protein Record.—This patient always reacted violently, with chill, fever, sweating and pain. He received ten injections (Fig. 3). There was no permanent improvement in the case. There was marked immediate improvement following the first injections. The bedside notes on this case may be of interest because of the marked reaction, with slight blood changes which, however, were otherwise characteristic.

Bedside Notes.—Jan. 30, 1918. The patient was injected yesterday with 1 billion typhoid bacillus intravenously at 10:30. He showed no reaction until 11:30, when quite a violent chill began. This lasted for about twenty-five minutes. At the end of this time the chill stopped; patient still complaining of being cold. This lasted for about an hour. At the end of this time he began sweating profusely. Patient's temperature began to rise a half hour after the injection, but did not rise markedly until five hours after the injection. At ten hours after the injection he reached his maximum temperature 103.8 F. A peculiarity of the leukocyte count was seen. The patient had been running a count between 8 and 9,000 in his control. Immediately after the injection

he showed a leukopenia, and four hours afterward he was back to normal again. Since then his counts have been about 1,000 below normal.

Jan. 31, 1918. The patient's fingers and toes are distinctly more flexible. He makes a fairly good fist and stiffness of the fingers before the injection has given place to distinct relaxation. He was unable to move the toes before the injection, and this morning all of the toes on the left foot move very perceptibly, while those on the right foot move more. There is little if any pain in the fingers, but there is still pain in the toes.

Feb. 1, 1918. The second injection was given at 10:30 a. m. The patient had no breakfast; 1 billion typhoid vaccine. At 11 o'clock pulse was fuller, more rapid, regular; at 11:35 patient began to feel chilly. At 11:40 patient

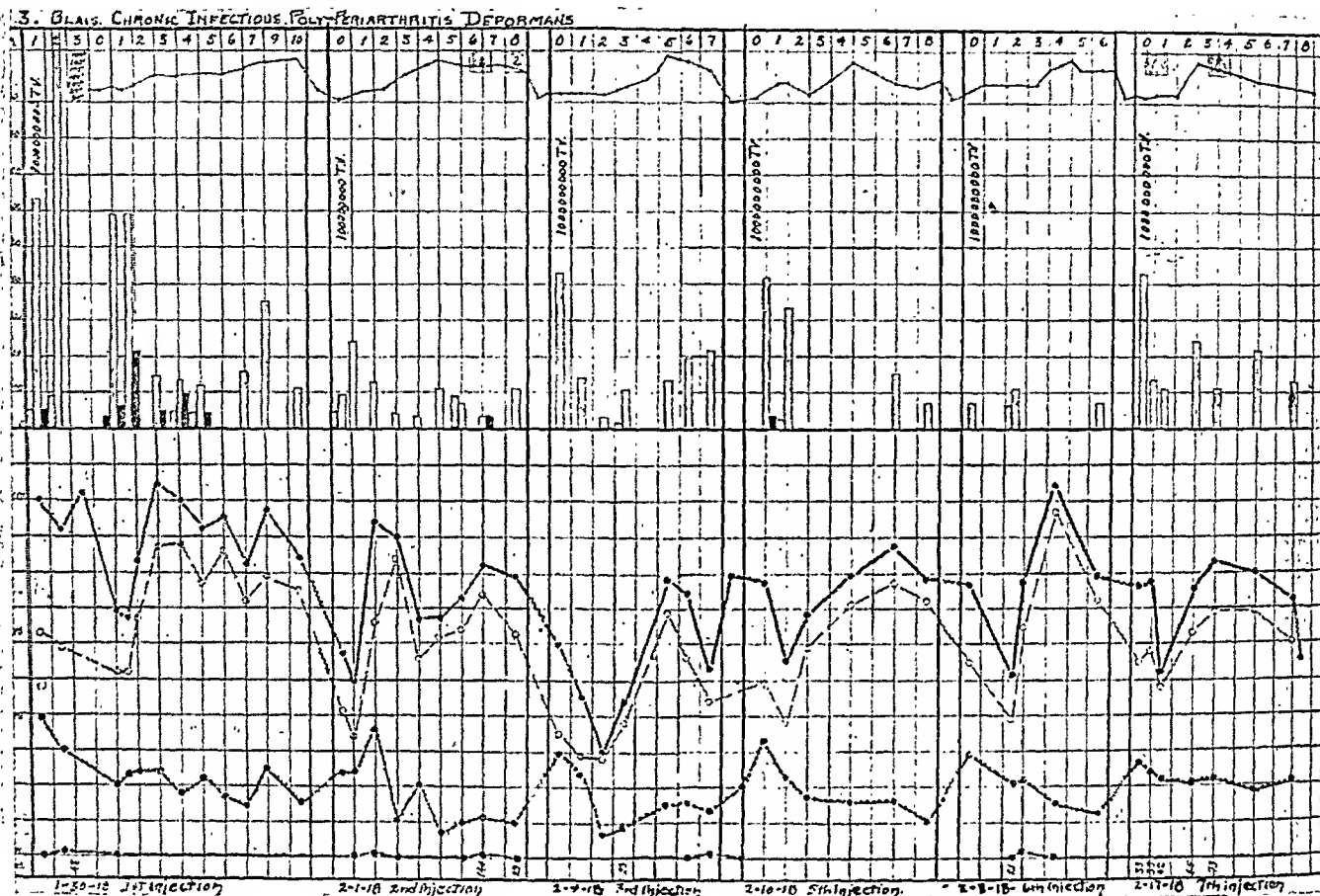


Fig. 3.—Case 3, Blais. Chronic infectious polyarthritides deformans.

was shaking severely and the skin was dry. At 12 patient shaking slightly, at 12:05 chill stopped. The chill lasted for half an hour. Patient now fell asleep. Twenty minutes after the chill stopped patient went into a profuse sweat which lasted for an hour and a half and he complained of feeling hot, much more than at the first injection. This was after the sweat was over, and the skin did not feel particularly moist. This morning there is no question but that the fingers and toes are much more flexible. The patient speaks of this himself. The pain is less marked. The highest temperature was 103.8 F.

Feb. 4, 1918. The patient was seen this morning and complained more of pain than he had at any time since the injection. He has a little more difficulty than was experienced two days ago in flexing the forearm.

Feb. 5, 1918. Patient himself says he is very much better this morning. He makes almost a complete fist with both hands and moves the toes of both

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feet, and the feet are very much better. He straightens his knees some better and flexes them fairly well, but the improvement is not so marked in these joints.

Feb. 6, 1918. He does not make quite so good a fist this morning; says his toes and his knees are better. Says his toes are as good as they ever were. He has stiffness in his hands and elbows.

Feb. 7, 1918. Preceding the injection the patient was unable to move his right arm any more than at the beginning; he could not move his left arm. The injection was given at 11:30; dosage 1 billion. The patient reacted by a chill; his temperature went to 104.8 F.

Feb. 8, 1918. Patient is able to move his right arm very freely in all directions. He makes a good fist in both hands. He says the pain in his arms is not in the joint but in the "muscles." The toes are moved freely; hands same. Patient is able to straighten his knees completely.

Feb. 11, 1918. Patient received his fifth injection yesterday. He feels worse this morning; has great difficulty in making a fist. The fingers are stiff; pain in both arms; is unable to straighten his knees.

Feb. 13, 1918. Examination before the sixth injection: The fingers of the right hand are greatly distorted. Patient is unable to flex or extend his fingers completely. Right elbow very sore and movement limited. Fingers of the left hand are extended straight and when flexed lack 2 cm. of reaching abductor pollicis muscle. The left elbow extends the same as the other, but flexion is more equal on either side; is able to extend right knee better than the left. He has movement of the toes.

Following the injection: Patient has noticed a slight improvement, as in previous injections. The chill was less severe than the previous one but he continued perspiring through the night. He is able to close the fingers of the right hand with effort (which he could not do before the injection). The right elbow seems less sore today. The left hand shows slight improvement in flexion of the fingers—within 1 cm. of adductor pollicis.

Feb. 17, 1918. Patient was given seventh intravenous injection today. He had a chilly sensation during the day but no severe chills. Perspiration was very profuse and continued well into the night. The pyrogenic reaction was marked.

Feb. 21, 1918. Patient is in a miserable condition this morning, as bad as at any time since entering the hospital. His wrists are swollen and he cannot close his fingers, and he moves the right arm only slightly and with considerable pain. His knees and toes are practicably immobile. There are no heart murmurs. The rhythm is regular. Because of the discomfort to the patient, further examination could not be satisfactorily carried out.

Feb. 28, 1918. Practically no beneficial results were obtained from the use of typhoid vaccine.

CASE 4.—*Multiple periarthritides deformans and chronic arthritis.*

History.—Shag. Indian girl, aged 12, entered the orthopedic department of the University Hospital because of multiple joint deformities. Transferred to the pediatric department Feb. 24, 1918, for examination and nonspecific protein therapy. Family history, very indefinite.

Past History.—Patient had never been able to walk; said she used to crawl on hands and knees, later used a wheel chair. She said her condition was the same at the time of examination as it had always been; had become neither better nor worse. She never went to school; was able to write some, but could not read. She had not had measles, chickenpox or smallpox, but had had mumps.

The patient had been living with her aunt. She insisted that the vaginal discharge had always been present. There was no burning urination or other symptom. Patient had a tendency to constipation; no nocturia; appetite was good.

Orthopedic Record.—Patient entered the orthopedic ward Oct. 27, 1917, as an emergency state case. No definite history obtained. The lower and upper extremities were deformed, due to arthritic process in the elbows, wrist, fingers, hip, knees, ankles and toes. The right hip was completely ankylosed, the left partially. The knee joints were both hypertrophied, while the surrounding muscular tissue was atrophied. The toes on either foot were deformed, producing hallus valgus deformity of both large toes. Several other toes were of the hammer type. There was ulnar flexion deformity of the fingers. The fingers showed hypertrophic joints and Heberden's nodes. The elbow joints were partially ankylosed so that the forearm could not be fully extended. On the posterior surface of either elbow were bursae, possibly due to the fact that the child had been compelled to creep on the forearms and knees. The

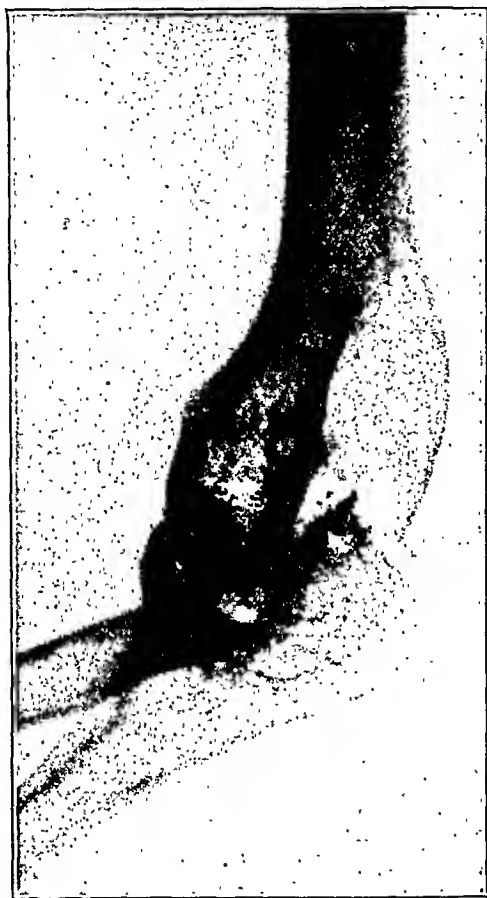


Fig. 4.—Case 4. Elbow showing the absence of epiphyses.

reflexes were normal; tonsils were enlarged; teeth in fair condition; lungs negative; heart negative.

Roentgen Report.—Stereogram of the pelvis and hips. The pelvis is irregularly deformed. There appears to be complete ankylosis of the left hip, while the right is not entirely ankylosed. There remains a plane of separation between the flat head of the femur and the acetabulum. The lesser trochanters are enormously enlarged. The femurs are hyperplastic. There seems to be ankylosis of the lower lumbar and no epiphyses are seen. Stereogram of elbow (Fig. 4) shows similar changes. This is not a true ankylosis but a marked deformity of the articular surfaces. The joint surface is V-shaped and the bony trabeculae are unusually distinct. No epiphyses. There is evidently some gross anomaly in development. We are unable to conceive of these changes as the result of an inflammation. Diagnosis impossible.

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Nonspecific Protein Therapy.—This patient received ten intravenous injections of typhoid vaccine. Each one was followed by a typical clinical reaction (Fig. 5). The patient felt so much better after each reaction that she begged for the next. She was always more supple and generally more comfortable. The patient made undoubted improvement. The joints were more relaxed; she moved about remarkably well in her bed, a thing she could not do before

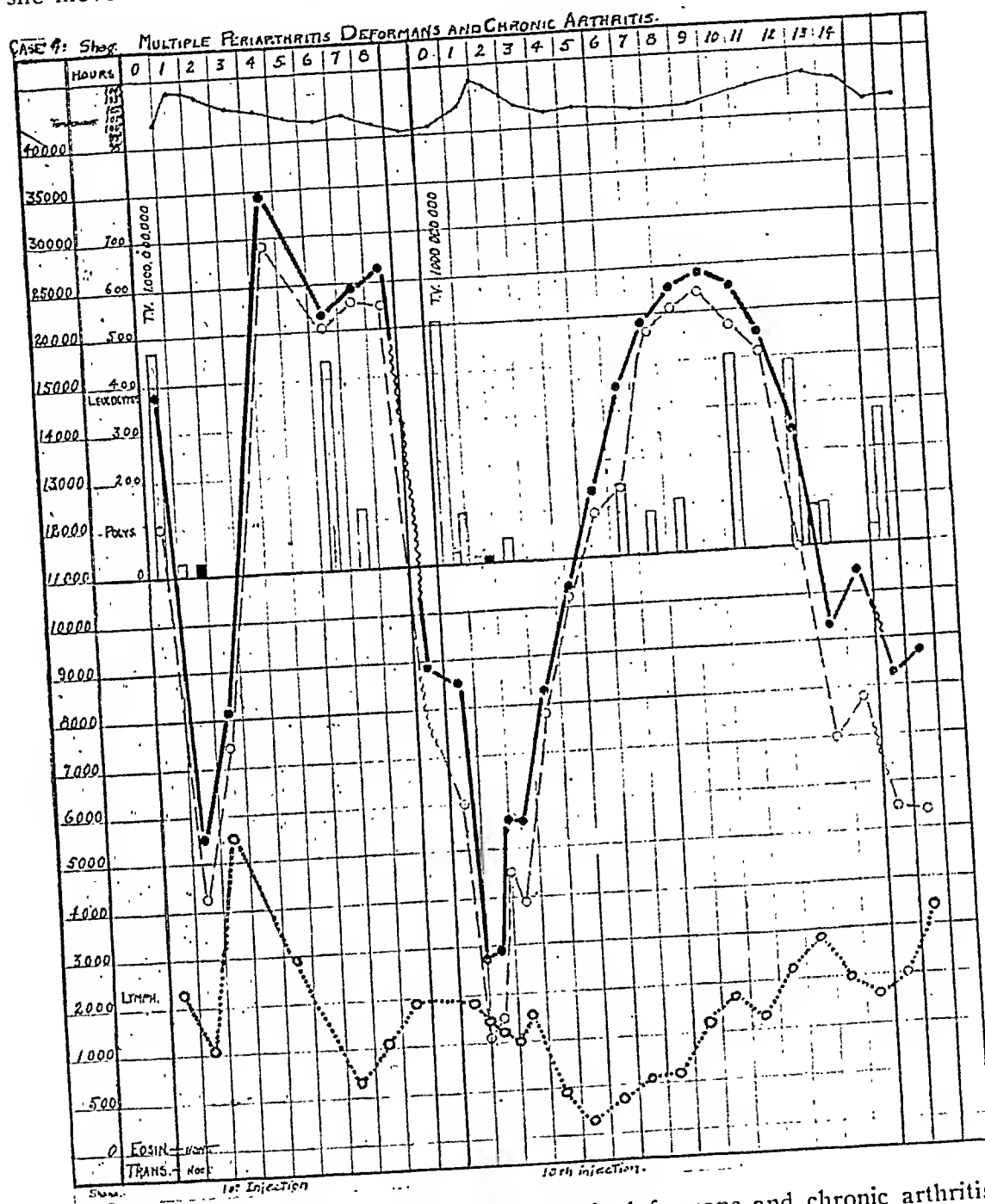


Fig. 5.—Case 4. Shag. Multiple periarthritides deformans and chronic arthritis. the treatment. She learned to knit and to wheel herself about the ward in a wheel chair. The structural bony changes were unaltered, but the joint stiffness was very much less marked. No perceptible change was noted in the vaginal discharge, which was still fairly profuse and of a whitish, catarrhal character. No gonococci were found on repeated examination. The reactions recorded are the first and tenth.

CASE 5.—*Acute rheumatism; joint swelling; no structural change.*

History.—Miss W., a nurse, aged 22, was admitted to the medical ward of the University Hospital Jan. 29, 1917, complaining of swollen and painful knees. In 1914, she had a severe attack of quincy, lasting for four weeks. The abscesses were not lanced. Since that time she had had frequent sore throats. In December, 1916, she had a severe attack of tonsillitis with fever for three days. Following her recovery she was well until Jan. 22, 1917, when her back became lame. On the 23d there was some pain in the left knee. The right

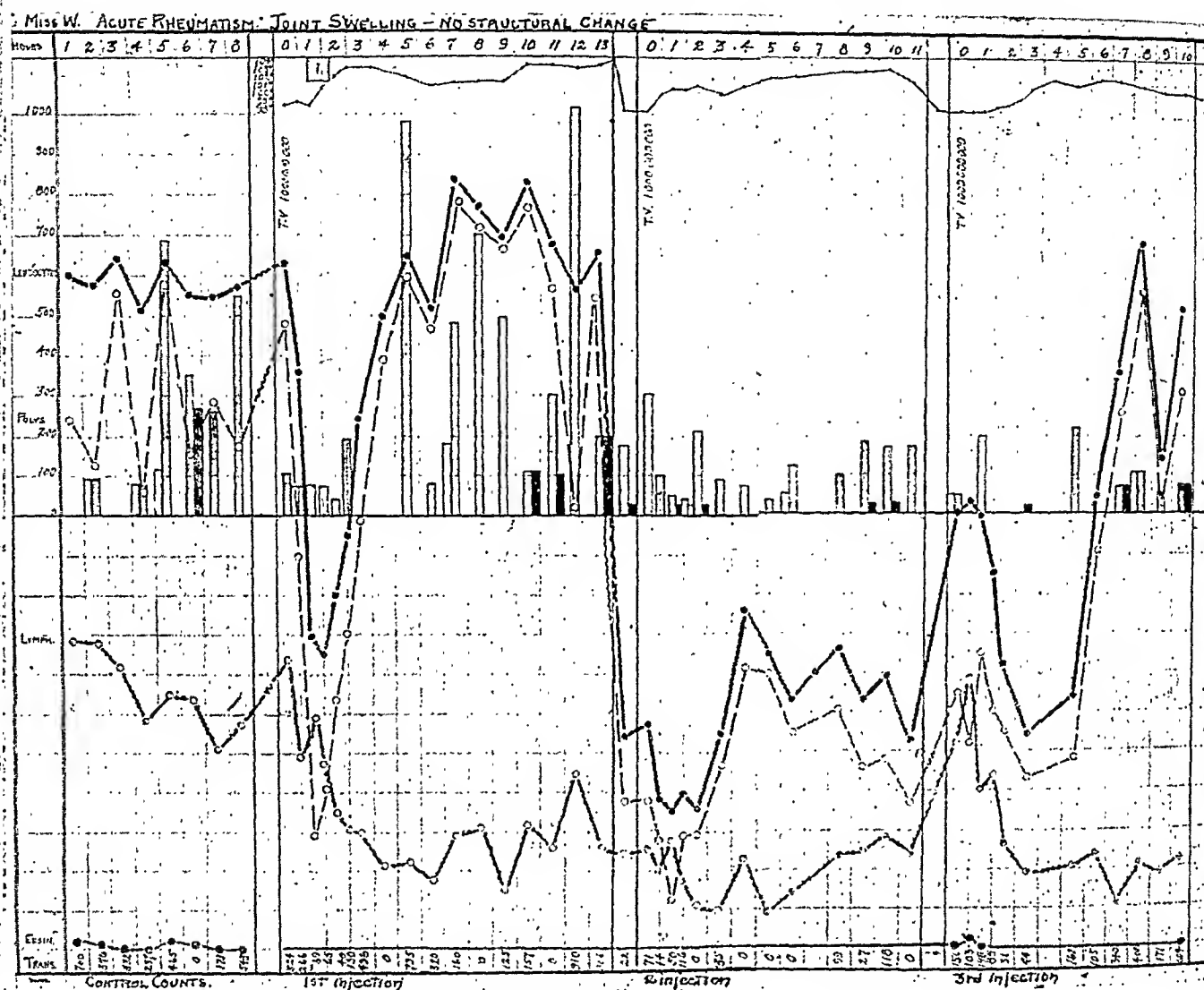


Fig. 6.—Case 5. Miss W. Acute rheumatism; joint swelling; no structural change.

knee was involved the following day. On examination both knees were swollen and tender but not reddened, and no fluid was demonstrable. There was slight swelling of the right ankle. The joints were warm and sweating. The tonsils were enlarged and septic. There were no heart murmurs. The patient was put to bed with the joints wrapped in cotton and given sodium salicylate, 160 grains per day. There was marked improvement under the salicylate treatment, and on Feb. 10, 1917, she was sent home to return for a tonsillectomy in several weeks. The last of March, 1917, the patient had her tonsils removed and six weeks later she had a slight attack of arthritis which cleared up in

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a week under sodium salicylate, 150 grains per day. From that time until December 21 she was well and gained 40 pounds. December 21, following a severe head cold, she developed pains in her joints. The joints involved were the knees, hips and elbows. Just before the attack of cold she noted that she had dyspnea and some pain at the base of the heart. Examination on entrance showed a definite mitral insufficiency and a murmur at the base in the pulmonic area, probably functional. Roentgenogram of the teeth was negative; of the sinuses, showed normal frontals, increased density in the right posterior ethmoid and a hazy, indefinite density in the right antrum, without changes in the bony wall. She was treated with salicylates and oil of wintergreen applied to the joints. She did not make satisfactory improvement, and Dec. 29, 1917, she was transferred to us for nonspecific protein treatment. On the day of the injection she was complaining of soreness and stiffness in the elbows and knees.

History of Present Attack.—December 6, patient reported a cold, headache, sore throat and general aching of the body. Temperature at 4 a. m., 100.4 F. Culture taken was negative. She returned to duty. December 22 she was unable to report for duty because of painful swelling of the knees. She was unable to walk. She made no satisfactory improvement on salicylate. No further foci could be found, and, for this reason, she was transferred to this department. The day of the first injection the patient was still complaining of soreness and stiffness in her joints, elbows and knees.

Jan. 22, 1918, the following note was made: "Left border of the heart is 10 cm. from the midline; right border $2\frac{1}{2}$ cm. Apex is felt in the fifth intercostal space, nipple line. Upper border is, apparently, on the third rib. Careful palpation reveals no thrills. The heart impulse is not marked. A double murmur is heard at the apex, giving the sensation of distance. Both sounds are heard. The murmur, particularly the systolic, is heard in the axilla. The diastolic murmur becomes louder toward the sternum, and is very loud and exhaustlike at the pulmonic area. The pulmonic second sound is definitely accentuated, and is not to any degree displaced by the loud murmur in the pulmonic area. The diastolic murmur can be heard all over the precordia. The patient is very much better after her last injection."

Roentgen Report.—Roentgenogram of the teeth negative; roentgenogram of the sinuses shows normal frontals, increased density in the right posterior ethmoids and a hazy, indefinite density in the right antrum without changes in the bony wall. Diagnosis, posterior ethmoiditis. Stereogram of the knee, good rays. These plates show the bones normal in outline, density, texture and relationship. We see no evidence of involvement of the bones or cartilages; a soft tissue lesion.

Nonspecific Protein Therapy Record.—This patient was given three intravenous injections of typhoid vaccine, 1 billion each, December 29, January 1 and January 18. The individual reactions are recorded in Figure 6. The patient's symptoms were some better after the first injection, and disappeared entirely after the second. Because of her heart condition she was allowed to be up only two or three hours a day until the 16th when she was up considerable. On the 18th she complained of being uncomfortable and unable to move her lower extremities. Six hours after the last food she was given her third injection. This cleared her symptoms up completely within twenty-four hours. There had been no return to date, May 21, 1918.

CASE 6.—*Hypertrophic arthritis.*

History.—Miss Wor., aged 22, stenographer, entered the University Hospital in the medical clinic complaining of swollen and painful joints and inability to walk.

Family History.—Mother had rheumatism and a chronic heart lesion.

Present Illness.—Began four years before admission with a gradual onset; first, there was sharp pain in the left hip and thigh, then in the right knee.

Nonspecific Protein Therapy Record—The patient did not improve under

salicylates and no focus of infection being found she was given 300,000,000 typhoid vaccine Dec. 10, 1917, at 1:25 p. m. This was followed by a chill beginning at 2 and lasting for twenty minutes; the temperature rose gradually, reaching a maximum of 100.8 F. at 5 p. m. There were no focal symptoms accompanying the reactions. The patient thought the knees and ankles were more flexible. Dec. 17, 1917. Patient was given two injections of 500,000,000 and 1 billion typhoid vaccine with the same reactions as the first. Dec. 19, 1917, she was given agar agar intravenously. Two minutes after the injection the patient complained of feeling queer, with tickling and choking sensations in the throat and tingling in the feet. She was extremely cyanotic, with an anxious expression. The pulse was small, weak and rapid. Her condition resembled shock. In fifteen minutes she felt better, but the cyanosis was still present. In one hour her condition was normal.

Jan. 7, 1918, she was transferred to us for intravenous typhoid vaccine. She was given a dose of $1\frac{1}{2}$ billion. Her temperature rose to 102.4 F., and was preceded by chill (Fig. 7). Her joint condition showed no permanent improvement after these four injections of typhoid vaccine, so she was returned to the medical department where subsequently she received three doses of Colles' serum. These injections gave a severe symptomatic reaction, but the temperature never rose above 102.2 F. After three injections she was markedly improved and able to walk.

CASE 7.—Atrophic arthritis.

History.—Mrs. McD., aged 64, entered the Cowie Hospital Oct. 18, 1917, complaining of pain in the knees and difficulty in walking. Duration, four and a half years.

Five years prior to admission the patient had gastric ulcer with hemorrhage from the stomach. Six months later there was a second hemorrhage, and since that time there had been pain in her knees which gradually became worse. Both knees were affected. They were swollen, and it was impossible completely to extend them. The pain was more severe on walking. No other joints were affected. At 14 the patient had a severe attack of inflammatory rheumatism lasting three weeks. The left side and knee were involved. Recovered with a heart lesion which was perfectly compensated. Had never had any trouble with her tonsils. Except for a tooth removed recently which had a small pus pocket at the root, there had been no trouble with her teeth. In March, 1917, the patient had a severe attack of laryngitis which was followed immediately by "sciatica." Twenty-five years ago the patient was in a railroad accident. Her sternum was fractured (?) and her back was injured, and has been weak ever since. Fifteen years ago she was treated for "catarrh of the stomach." This was the first record of stomach trouble. Seven years ago the patient had ptomain poisoning from oysters, and during the following year she lost 35 pounds. Fifteen months after this attack she had her first hemorrhage of the stomach (March, 1912). The second hemorrhage occurred in November, 1912. For the two years following she was troubled with pain in the epigastrium of a sharp, shooting character, occurring four hours after eating. In the fall of 1917 she had an acute attack of stomach trouble, and at the same time her knees became worse. She had never noticed any fatty stools. Menopause at 50. Had a single severe hemorrhage which was repeated the second month. No other difficulty.

Family History.—A daughter is said to have had gastric ulcer. One son has had medical treatment for gastric ulcer. The patient's mother had severe stomach symptoms and one sister had "gastric ulcer."

Physical Examination.—Large frame. Fairly well developed musculature; muscles soft. Panniculus thick all over the body. Slight edema over both ankles. Inguinal glands just felt; otherwise glands were negative. Circumference of the knee, 44 cm. both sides. Patella reflexes not obtained, probably due to position; elbows prompt.

Four days later the metacarpal-phalangeal joints were involved. Joints in the hands and fingers had been painful for three years; the ankles were affected one year prior to admission and since then she had had difficulty in walking. The past three weeks the jaw had been involved.

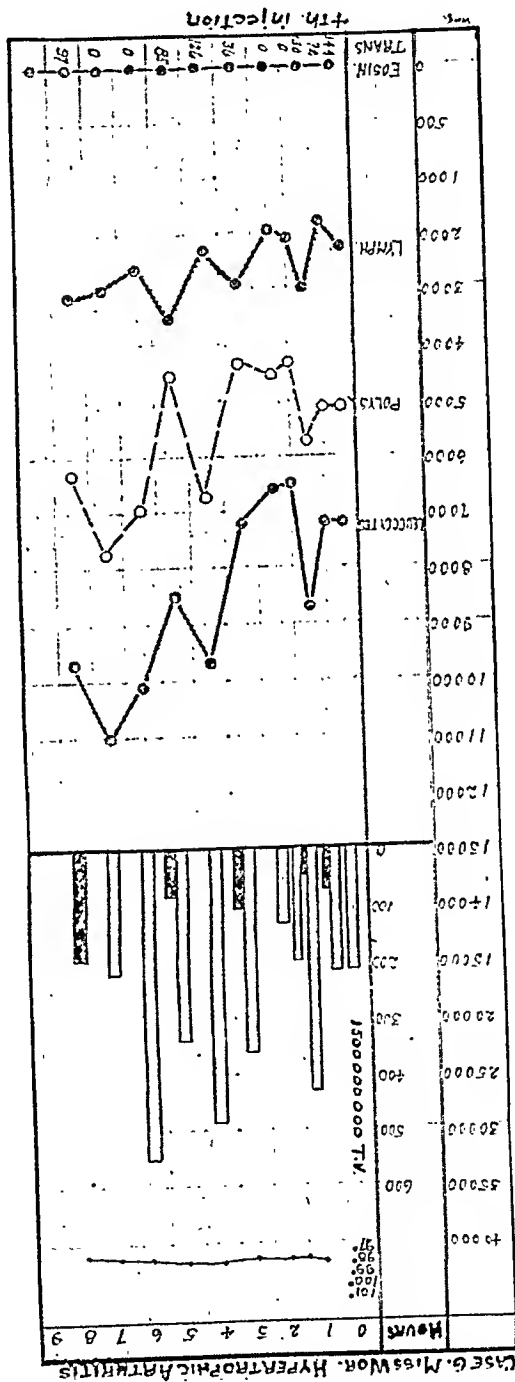


Fig. 7.—Case 6. Miss Wor. Hypertrophic arthritis.

Examination.—Patient was of moderate build with good musculature. The apex of the heart was in the fourth intercostal space and the sounds were clear and distinct, with no murmurs. The extremities showed hypertrophy of all the joints, especially the ankles and finger joints. There was beginning ulnar flexion of the latter. The picture was typical of hypertrophic arthritis.

Lungs: Increased vesicular inspiration all over (moderate degree of emphysema); no other adventitious sounds. Patient had been short of breath for five or six years.

Heart: Apex difficult to locate, apparently the same as the left border—11 cm. from the midsternal line just outside the mammary line. Right border

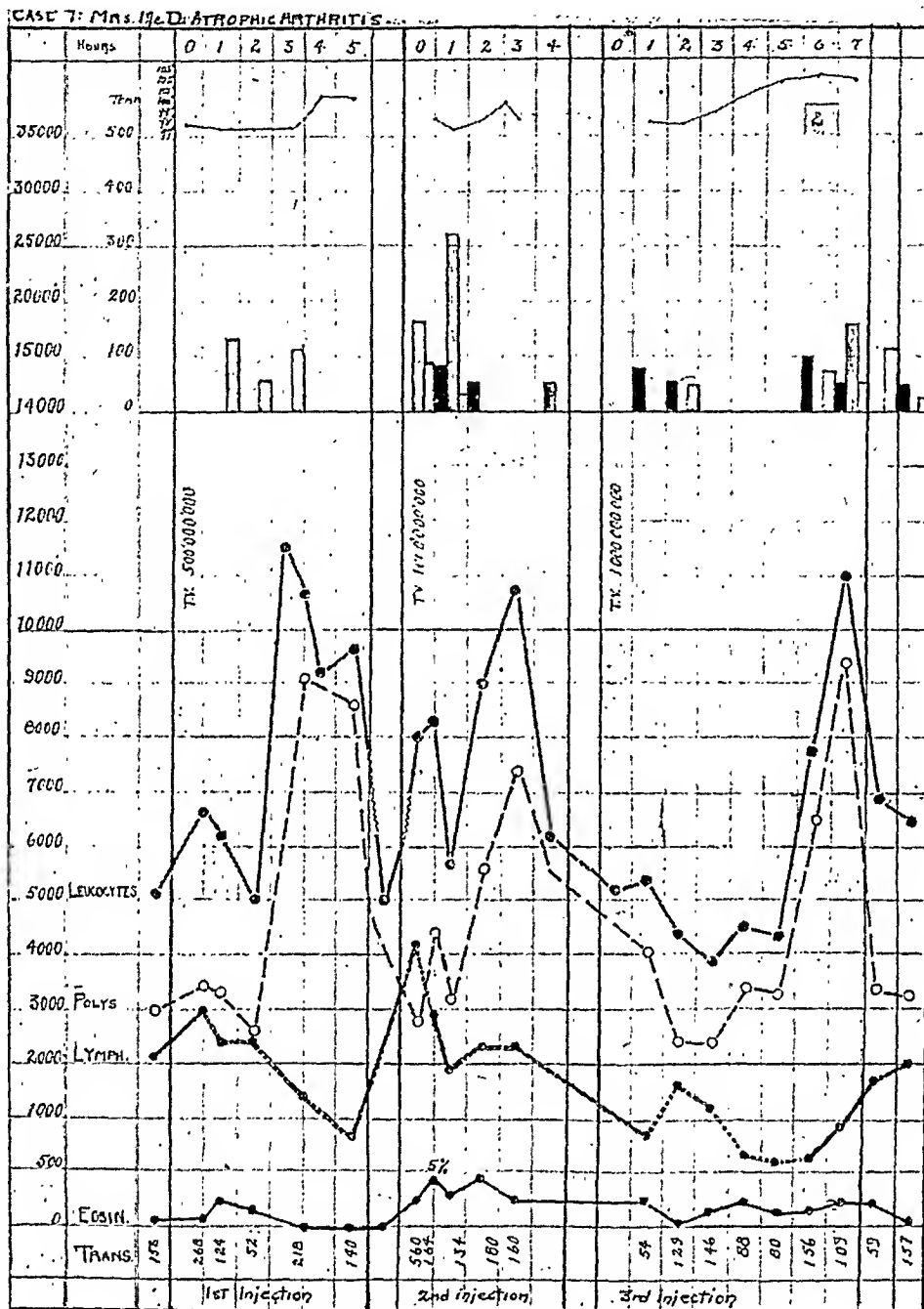


Fig. 8.—Case 7. Mrs. McD. Atrophic arthritis.

2.5 cm. Upper border on third rib. Aortic arch did not seem to be increased. Heart impulse moderate. No thrills. First strike of the apex about normal; it was followed quickly by a very distinct, short, blowing murmur which terminated in a flapping second sound. It was difficult to differentiate whether the murmur followed the first sound and was part of it, or whether it was

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part of the second. The murmur was not transmitted to the sternum, was not well transmitted into the axilla, but could be heard. Pulmonary second sound was, possibly, slightly accentuated and louder than aortic second sound. Aortic area seemed to be negative. The first sound in the carotid was very plainly heard, somewhat roughened, but no thrill could be felt on reexamination. Blood Pressure: Systolic, 125; diastolic, 70; pulse pressure, 55. The pulse is regular, 78, fairly easily compressed; felt slightly after compression; not particularly tortuous; negative. The patient had been conscious of the ankle swelling. She had no characteristic pain in the left arm, but complained of some rheumatic pain in the right shoulder. No chest tightness.

Abdomen, negative.

Blood: Red cells, 5,180,000; white, 5,500; hemoglobin, 80 per cent. (Talqvist). Polynuclears, 56; small lymphocytes, 29 per cent.; large lymphocytes, 8.5 per cent.; transitionals, 2.5 per cent.; eosinophils, 1 per cent.; mast cells, 1.5 per cent.

Urine negative

Stomach functions negative.

Roentgenographic Record.—"Lateral stereogram of each knee and an antero-posterior including both knees. The pathology is virtually identical in both knees. Superficially the most striking feature is the marked osteophyte formation at the margins of the articular cartilages, but careful observation demonstrates a marked erosion of these cartilages with lateral luxation. The erosion is most marked over the internal condyle."

"Diagnosis, chronic atrophic arthritis."

Nonspecific Protein Therapy.—Nov. 7, 1917, the patient received the first intravenous injection of typhoid vaccine, dosage, 1 billion. At the end of three hours she had a marked chill and suffered from severe pains localized in the back, legs and knees and an increase in temperature (Fig. 8). November 8, she was given her second intravenous injection. The chill in this reaction was delayed for four hours. It was very severe. The maximum temperature was only 100 F. Pain was very severe. On the 12th she received her third injection; the chill followed in three hours with a rise in temperature to 102.4 F. following it. After the nonspecific protein therapy the soreness disappeared from the knees and they were straighter, although the difficulty in walking still persisted.

CASE 8.—*Hypertrophic arthritis of spine.*

History.—Mrs. B., housewife, aged 46, entered Cowie Hospital because of neuralgiform pain, occurring in remittent attacks involving the right leg and thigh and the posterior cervical region. Family history negative.

Past History.—The attacks of pain were present for eight or nine years, the first attack lasting a year. At this time she had sharp shooting pains in the chest and soreness in the left arm. There had been remissions lasting a year or more when she had felt normal. For the previous two years the pain had been localized during the attacks in the right leg and hip and in the back of the head and neck. There was pain and soreness on pressure which was aggravated by walking or standing. Because of the pain she found it difficult to stoop over.

At the age of 18 she had an infected fallopian tube with abscess formation. The first child, born about twenty years previously, was delivered by high forceps, and the patient was badly lacerated. In 1913 one ovary, one tube, and the uterus were removed. This operation improved the patient's headaches and she was distinctly better following it. She has always been constipated and believes that the attacks of neuralgiform pain follow a period of constipation.

Physical Examination.—Examination showed a small, well built woman, who looked about 35 years old. Physical examination was negative except for absent pharyngeal reflex, inframammary tenderness, slight tremor of the

extended hands, and tender points along the sciatic nerve, the second, third and fourth cervical vertebrae and the lumbar vertebrae. The heart on Aug. 30, 1916, showed the apex in normal place and the heart sounds negative. In November, 1916, examination showed apex and outlines normal, marked pulsation of the neck with slight thrill and the short soft puff which was not transmitted was heard at the apex. The pulse for this time was 104 F. Aug. 6, 1917, the heart was negative.

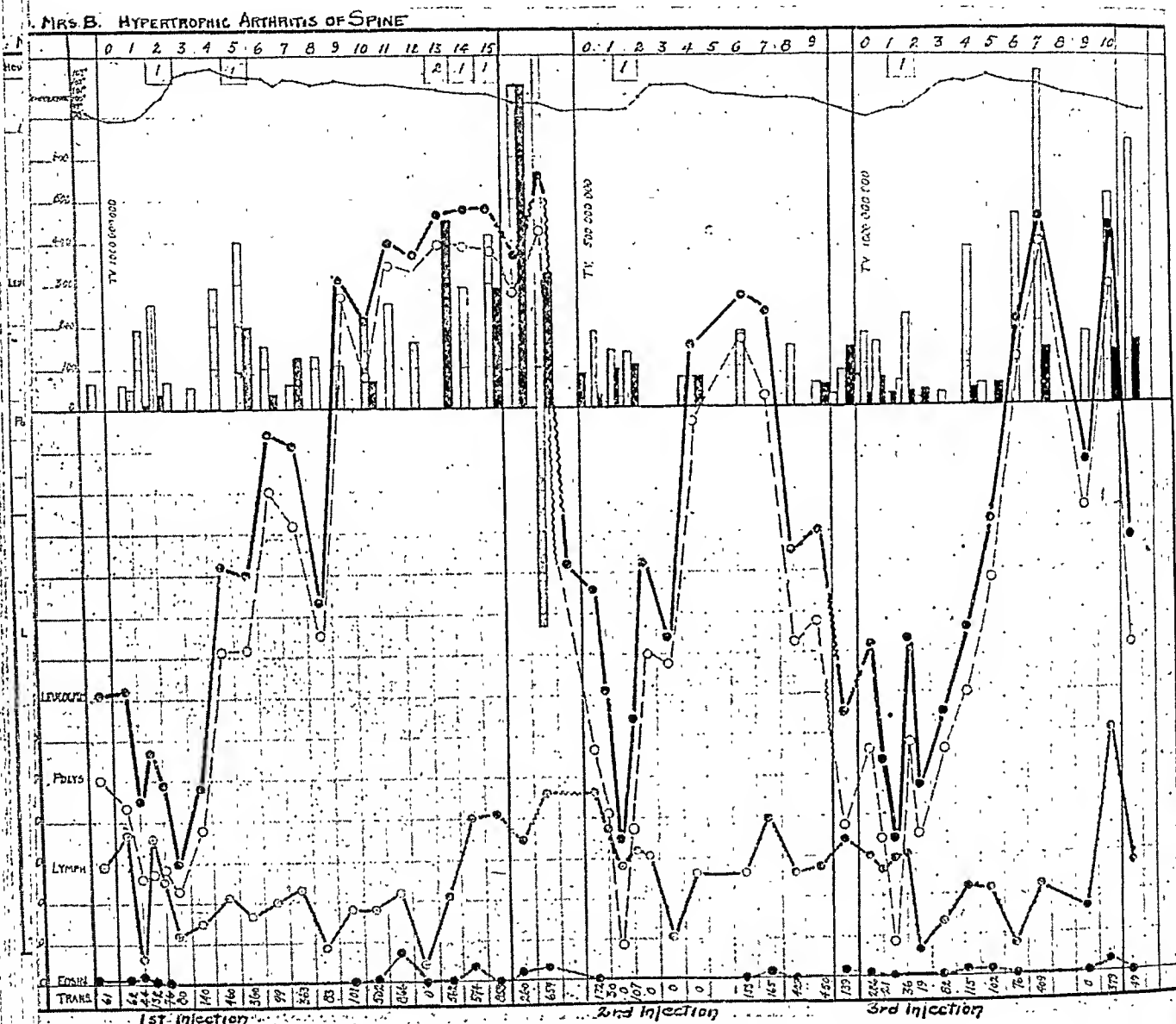


Fig. 9.—Case 8. Mrs. B. Hypertrophic arthritis of spine.

Neurologic examination showed areas of hyperesthesia on the right leg and thigh corresponding to the cutaneous distribution of the first, second, third and fourth lumbar roots and the first sacral. The upper boundary of the hyperesthesia was two finger breadths above the pubes and extended in a curved line to the lower dorsal vertebral spine. The lower limit extended diagonally across in front of the leg, involving a small semicircular area on the inner central aspect of the sole of the foot. There were pain points along the

course of the sciatic nerve. A diagnosis of radiculitis of the lumbosacral plexus was made and a roentgen-ray examination was recommended.

Roentgenographic Report.—A stereogram was made of the lower lumbar and upper sacral region. These were satisfactory roentgenograms, from the third lumbar to the sacrum, including both sacroiliac joints. The spine was straight and the fifth lumbar was of the free standing normal shape. The pathology appears to lie in the anterior or intercentral articulations of the lumbar spine. The findings consist of a roughening and accentuation of the upper and lower surfaces of these centra, with a distinct lipping at the angles. There is also a slight lipping at the lower margin of the iliosacral articulations. The majority of the pathology, however, is in the spine. The hip is negative. This is an anterior spinal arthritis.

Nonspecific Protein Therapy Record.—Feb. 7, 1918, the patient received intravenous injection of typhoid vaccine, dosage 1 billion. Within a half hour she was chilly and complaining of severe headache and backache (Fig. 9). Within three hours her temperature had risen to 104 F.; she was very restless, nauseated, and delirious. Respirations were very short and rapid and she was cyanotic. Because of the severity of the reaction she was given on the second injection, February 11, only 500,000,000 as a dose. This was followed within half an hour by a severe chill and headache; the reaction was completed by 6 o'clock. The temperature did not rise as high as might have been expected from the severity of the chill. February 13, she was given her third and last intravenous injection of 1 billion typhoid vaccine. This was followed by a very severe chill lasting for twenty minutes, a marked increase in temperature and at the end of three hours delirium. She localized the pain in the occipital region, in the back and in the right leg and thigh. During her delirium she complained of having two heads, both of which ached. Temperatures taken showed the axillary temperature to be a degree and a half below the temperature taken in the right popliteal space. The temperature over the back of the neck was perceptibly higher than that of the face. On the day following the injection the patient found that she could stoop over without pain and since that time the spine has remained more flexible. She was told the intravenous injections might arrest the arthritic process but could not repair structural damage already done.

CASE 9.—Gonorrheal vulvovaginitis.

History.—Frances C., a girl, aged 2, entered the pediatric department, Jan. 4, 1918, because of profuse vaginal discharge.

Family History.—The mother denied vaginal discharge in herself and other little girl.

History.—Has no bearing on the case.

Present Illness.—This started four weeks prior to admission; yellow white vaginal discharge; genitals excoriated and red, causing much pain on micturition. Smear positive for gonorrhea.

Physical Examination.—General examination negative.

Genitals: There was a very slight excoriation of the external parts; marked vaginal discharge of yellowish white pus. Anus normal and clean.

Vaginal smear positive. Wassermann negative. Neisser complement fixation positive Jan. 7, 1918. Neisser complement fixation negative Jan. 25, 1918.

Nonspecific Therapy Report.—This patient received five intravenous injections of typhoid vaccine; seven partly intravenous and partly intramuscular. With the exception of the final dose of 500,000,000, the dosage was one billion. The injections were given January 9, 12, 19, 25, 28, and February 1, 4, 7, 9, 11, 13, 17. Those in italics were partly intravenous and partly intramuscular. It was almost impossible to get a vein in this child. Most of the intravenous injections were given into the jugular. Marked leukocytic reactions followed each injection in which counts were made excepting the fifth recorded. The

temperature reaction was not marked; 102 F. recorded only once. The patient suffered no inconvenience whatever from the injection (Fig. 10).

There was no lessening of the vaginal discharge following the first injection. After the third injection the nurse was certain the discharge was distinctly less, but it still had to be charted profuse (3). After the sixth injection the discharge was distinctly less, now charted (2).

Two days later very little discharge could be obtained for a smear; only a few leukocytes and a few epithelial cells were present and a few intracellular cocci. After the ninth injection the discharge was still slight in amount and from then on there was very little visible discharge. The case at the time

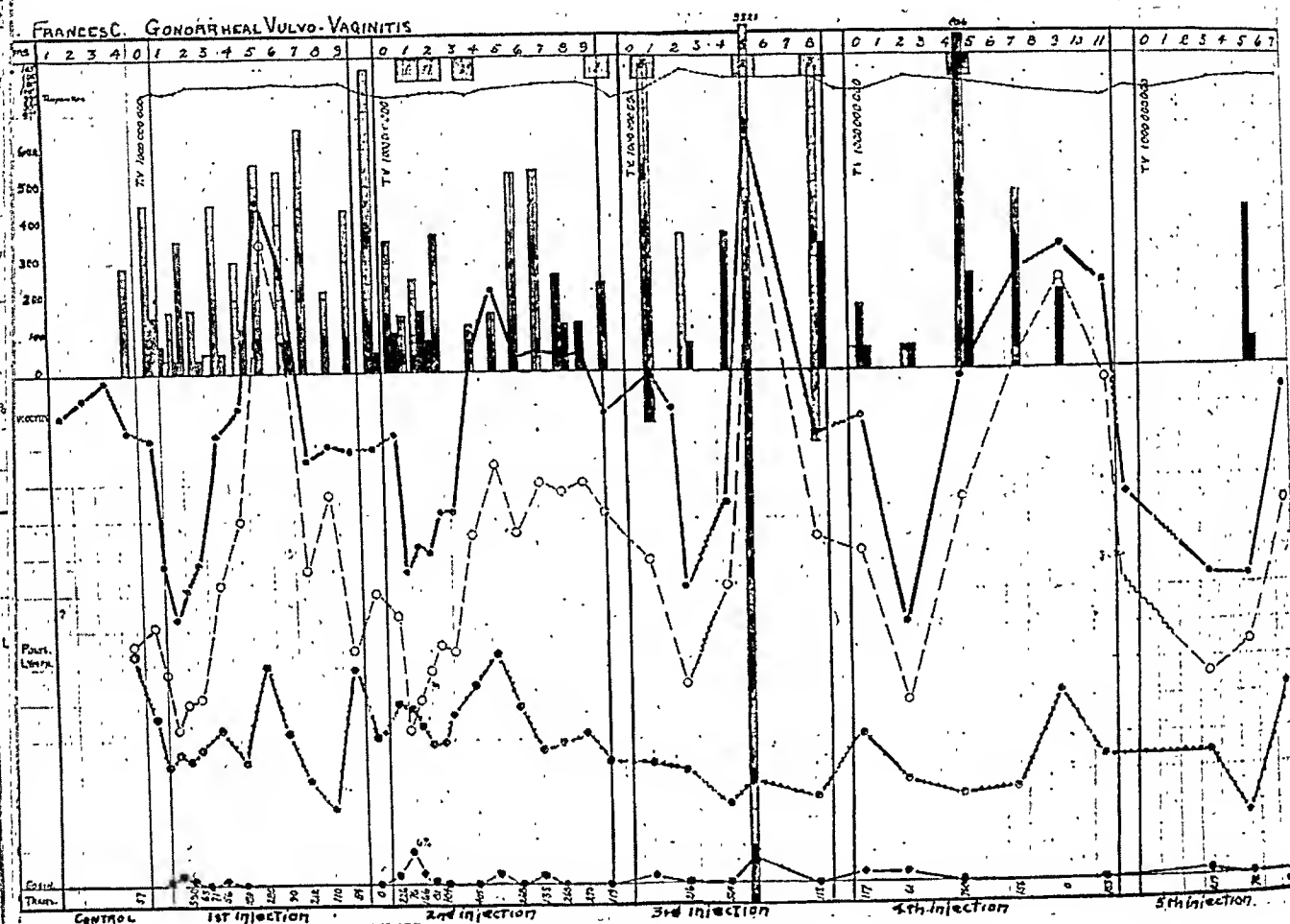


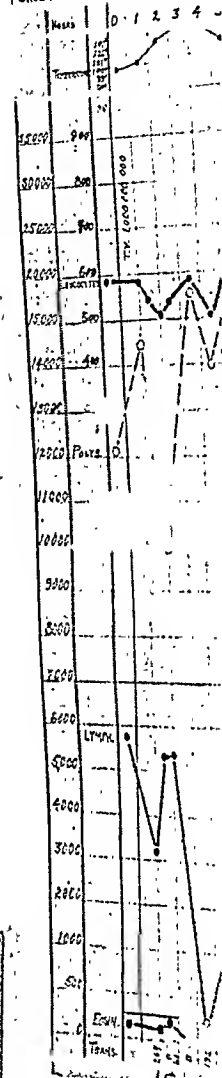
Fig. 10.—Case 9. Frances C. Gonorrheal vulvovaginitis.

of the report was practically clear without any further treatment. (Note.—July 1, patient continued to have a slight discharge and occasionally intracellular organisms were found.)

CASE 10.—Suppurative mastoiditis with chronic pulmonary tuberculosis.

History.—Frei., a schoolboy, aged 9. The patient came to the University Hospital Oct. 17, 1917, because of double discharging ears. The temperature was normal. A double mastoid operation performed Oct. 18, 1917. The patient reacted well. There was a slight temperature reaction after the operation, but this subsided on the 21st and remained normal until the 28th, from which time until November 5, when he was referred to the pediatric department, it varied from 100 to 102 F. Aside from the discharging ears our examination at this time was negative.

Case 10: Frei. SUPPURATIVE



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Examination.—November 4, the patient was referred to us because of continued elevation of temperature ranging from 100 to 102 F. in the afternoon, returning to 99 in the morning. At this time we were unable to find any definite signs in the heart and lungs. Lumbar puncture gave clear fluid under increased pressure; about 20 c.c. came away. Total cells 650, all lymphocytes. Nonne, Noguchi, alcohol and Fehling tests negative. The blood pressure was found to be negative.

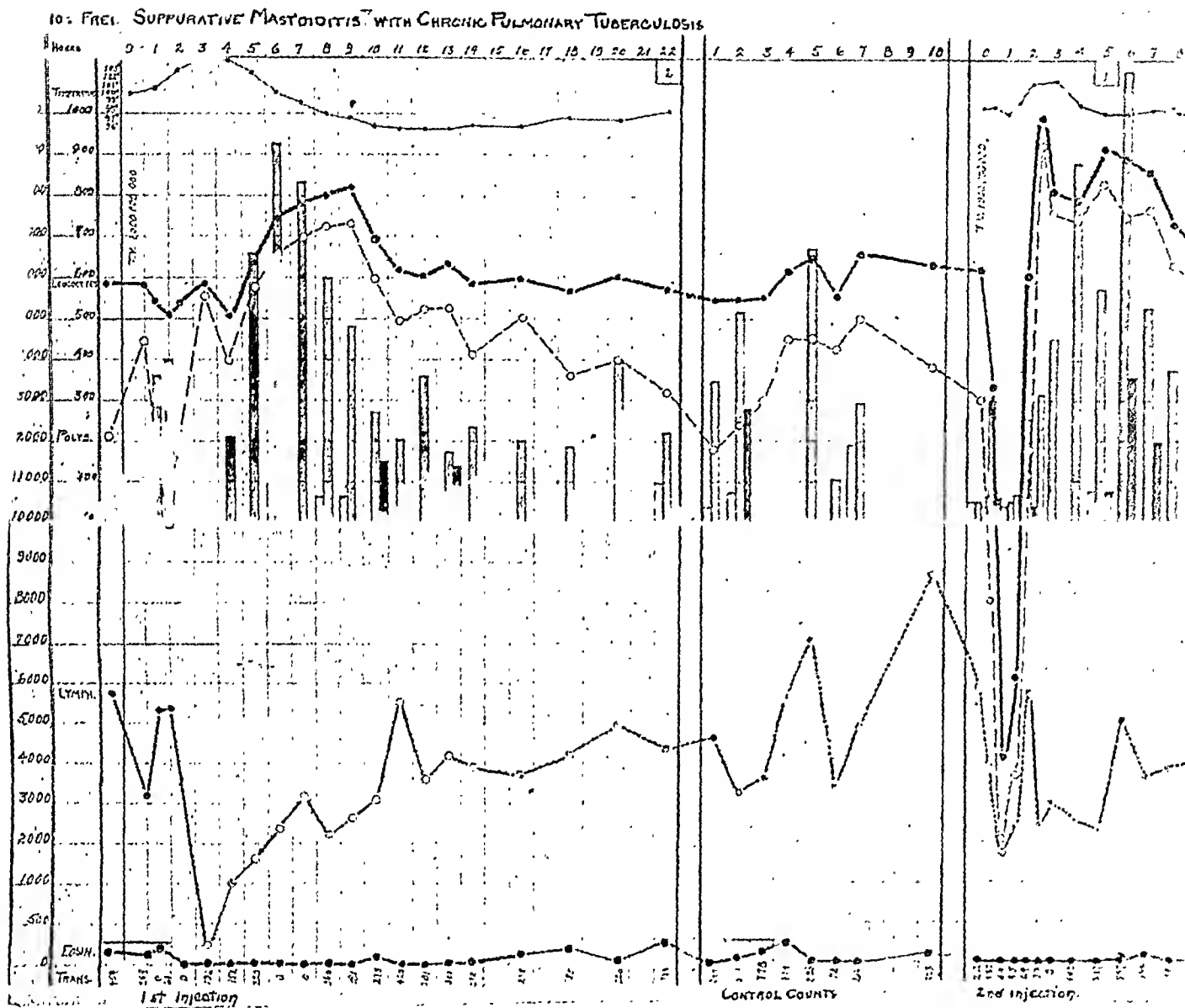


Fig. 11.—Case 10. Frei. Suppurative mastoiditis with chronic pulmonary tuberculosis.

December 13, referred again; at this time the heart was 3.5 by 8 cm. Roentgen ray showed cardiac enlargement over previous plate. Sounds negative; no murmur. Lungs: Low down in the right axilla there was slightly impaired resonance; exaggerated vesicular breathing, an occasional r  le. Dulness in the right back below the angle of the scapula; bronchovesicular breathing over this area; increased whispered voice. Many r  les. From now on definite chest signs were always present. A diagnosis of pulmonary tuberculosis was made on the physical finding of tubercle bacilli and by the roentgenogram.

This case was selected because of the suppurating mastoid, to see if any effect could be produced on the discharge, and to determine what effect the typhoid vaccine (intravenous injection) would have on the blood in this condition associated with tuberculosis.

Nonspecific Protein Therapy Record.—A first injection of 500,000,000 typhoid vaccine was given Dec. 21, 1917. It was followed by a chilly sensation at the end of one hour and nausea at the end of three hours. The temperature rose to its maximum of 105.4 F. three hours post-injection (Fig. 11).

The second injection was given Jan. 1, 1918, at 7:30 a. m.; the dosage was 1 billion; this was followed in two and one-half hours by a slight chill.

Two days after the injection the discharge from the ears had practically ceased, and a week later the department of otology found no discharge when the wound was dressed. The process was chronic and of three months' duration.

MOVEMENT OF NORMAL CELLS INDUCED BY FOREIGN PROTEIN

The Leukocytes.—Following an injection of typhoid protein there is almost invariably a decrease in the total leukocyte count. Commonly this decrease amounts to a distinct and often to marked leukopenia, but not always. In Cases 6 and 9, the leukocytes never went below normal. In Cases 1, 3, 4, 5, 7 and 10 the leukocytes did not go below normal until the second or third injection. This decrease in the leukocyte count in our cases varied from 1,600 in Case 6 to 16,000 in Case 10. The leukopenia usually immediately follows the injection. In twenty-nine reactions it occurred at the following hours.

Hours	1/2	1	1 1/2	2	2 1/2	3	Total
Number of Reactions.....	2	11	5	7	0	4	29

A reversal occurred in five cases (4, 5, 7, 8, 9). Following the leukopenia there is always a rise in the leukocytes. This occurs whether the leukocytic movement is above or within the normal limits. The leukopenia in the four children studied was not as low as in the adult cases, 5,000 being the lowest count. The greatest upward excursion from the lowest point reached to the height of the reaction was 33,000. The highest induced leukocytosis above the control was 29,000. The height of the leukocytes is usually reached in from four to nine hours after the injection. In twenty-nine reactions the height was reached at the following hours:

Hours	1 1/2	2 1/2	3	4	5	6	7	8	9	10	11	12	15
Reactions	1	2	3	5	3	2	7	2	3				1

In one case, No. 8, the last observation was made at the fifteenth hour, but the reaction continued throughout the next two days, when it reached its height, 35,000. By reference to the charts it will be observed that intercurrent drops or pseudocrises may appear in the leukocyte curve. The movement downward may be as great as 4,300 (Case 8). One might thus be easily misled and think the leukocytic reaction was over when, as in this case, the most marked changes were to come many hours later — numerous myelocytes, atypical cells

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and nucleated reds. The end of the leukocytic reaction is usually characterized by a critical fall.

Influence of Size of Dose on the Reaction.—On three occasions a 500,000,000 dose was given. In two of these the reaction was distinctly less marked; in one, a first injection, the reaction was the greatest. We have observed this many times in the simple clinical reaction, and at times when accidentally only part of the injection went into the vein.

The Polymorphonuclears.—The polymorphonuclears generally follow the total leukocyte curves pretty closely (Figs. 1, 5, 6, 9, 11), excepting at the time of the leukopenia, when there is very frequently a reversal. This reversal always precedes a prompt rise in the leukocytes (Figs. 5, 6, 8, 9, 10). The polymorphonuclears induced by the injection of the foreign protein took the nuclear stain after the fashion of new cells, as shown by the chromatin network staining very distinctly. Our attention was frequently called to the large size of the nucleus. We have not as yet made any Arneht counts. This question is of interest because of the shift to the left in typhoid fever.

The Lymphocytes.—In all cases, except Case 9, the large lymphocytes almost invariably disappear from the blood at some time during each reaction. The small lymphocytes, on the other hand, never completely disappear. There seems to be no relationship between the appearance of atypical large lymphocytes and the disappearance of the normal large lymphocytes; for example, in Case 3, first reaction, the relation of atypical large lymphocytes to the normal lymphocyte is as follows:

Hour	1	2	3	4	5	6	7	8
Normal	28	0	90	40	85	71	44	0
Atypicals	52	94	45	40	0	142	131	37

In four cases (1, 3, 7, 8) the number of large lymphocytes at times exceeded the number of small lymphocytes. In three of these cases (1, 3, 7) this reversal of the normal relationship does not occur until after the first injection. In Case 8 it occurs late in the first reaction. Delany,⁶ and also Krause,⁷ found the large lymphocytes equalled or exceeded the small lymphocytes in a differential count of malarial blood. This was so constantly present that Delany considered it as diagnostic as finding the plasmodium.

The total lymphocyte count in normal blood ranges between 1,500 and 2,200 per c.mm. Following an injection of typhoid protein there is almost invariably a decrease in the total lymphocyte count, almost immediately after the injections. This may only be slight, but the

6. Delany: Brit. M. J., March 28, 1903.

7. Krause, W.: J. A. M. A., 43:1202. 1904.

movement downward is nevertheless present. There is one exception, Case 3, reaction 1. Out of 29 reactions a lymphopenia occurred in 24. The lowest recorded is 200 (Case 4, second reaction). There were 10 reactions below 500 in 6 cases (1, 3, 4, 5, 8, 10). A lymphocytosis occurred in 21 reactions out of the 29; of these only 9 rose above the initial count. The highest lymphocytosis initiated by the injection was 8,800 and occurred during the interval between the first and second injections in Case 10. This patient had pulmonary tuberculosis and had an initial lymphocytosis of 5,800. In 7 cases (1, 3, 4, 5, 8, 9, 10) there was a lymphocytosis in the control, varying from 2,800 to 5,800. In 15 reactions the final lymphocyte count was lower than the initial count preceding the injection.

A decrease in the number of lymphocytes followed the chill in 23 out of the 29 reactions. This occurred in all the reactions in children. In no case do we get the immediate rise following the chill. This calls to mind the work of Rause on struggle lymphocytosis in which we have been interested. In dogs during marked struggle he found an increase in the lymphocytes. The chills in some of our reactions were so violent that we were looking for a similar increase in the lymphocytes, but it did not occur.

The Transitionals.—The total number of transitionals in normal blood ranges between 230 and 380, 3 per cent. and 5 per cent. In twenty-five reactions the transitionals ran below the normal; four of these showed an initial low count. In thirteen reactions the transitional count was above normal, two of them having an initial high count. The highest count is 866—3.5 per cent.

The Eosinophils.—In two cases only did the eosinophils show an increase, and this increase was only slight — Case 7, second reaction, 5 per cent., or a total of 400 cells; Case 9, second reaction, 6 per cent., or a total of 450 cells. The eosinophils, indeed, were conspicuous by their absence. This is strong proof that the reaction is not of an anaphylactic nature. In Cases 7 and 9 the increase came, in each case one-half hour after the second injection, suggesting an anaphylactic response to the previous injection. In Cases 3 and 5 they were present in the control and almost invariably absent during the reaction.

OCCURRENCE OF ABNORMAL CELLS

The Myelocytes.—Myelocytes were quite regularly found after the injection, twenty-four out of twenty-nine reactions. They were rarely present in the controls. In one case (8) a total of 800 cells were found. The basophil myelocyte was most frequently encountered. Myelocytes most frequently made their first appearance very soon after the injection,

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tion, in from one-half to one hour. Of the twenty-four reactions in which they occurred they appeared at the following hours.

Hours after Injection..	1½	1	1½	2	3	4	5	6	7	10	Total
Reactions	1	10	2	3	0	3	2	0	2	1	24

The Nucleated Red Cells.—Nucleated red cells were found in seven out of the ten cases; both megaloblasts and normoblasts were found. Their appearance was not necessarily associated with the appearance of myelocytes. This is interesting in view of Stockard's⁸ conclusion that "vascular endothelium erythrocytes and leukocytes though arising from mesenchyme are really polyphyletic, each with a different mesenchymal fundament or anlage, and if one is destroyed the others cannot replace it." That is, if the fundament producing myelocytes is destroyed, nucleated reds may still be manufactured but the myelocytic function can never be recovered. That the nucleated reds do not necessarily appear at the same time as the myelocytes might lead one to argue that the same stimulus reacts differently on two different "fundaments."

The Platelets.—We have been impressed with the large number of platelets present in the reaction smears. We were unable to make systematic counts. The morphology of these bodies was frequently quite remarkable;⁹ large sized well preserved ones were quite numerous. In Case 7 the plates were at times from one-half to two-thirds the diameter of the red corpuscles with distinct collections of nuclear matter, and at times a reticulated cytoplasm. Similar platelets were seen in several other cases.

Very early in the reaction we observed a stage when it was difficult to obtain a complete count from a single stab of the finger, owing probably to increased coagulation time (Cases 1 and 8 particularly).

Duke¹⁰ has observed after the administration of small doses of typhoid vaccine an increase in the number of the platelets; after large doses, a fall in the curve or a rise followed by a fall. In a typhoid inoculation he believes the effect is irritant (increase) and a toxic dose is not reached, while in typhoid fever the irritant dose is exceeded and a reduced count is the rule.

The Spectroscope.—Early in our work we became impressed with the cyanotic appearance in some cases and particularly a darker appearance in the blood when drawn into the pipet. This was most marked in Cases 7 and 8. In Case 6 intense cyanosis followed an intravenous injection of agar agar. This suggested the advisability of spectroscopic examination to detect the presence or absence of reduced hemoglobin.

8. Stockard: Am. J. Anat., 18: 1915.

9. Similar platelets have been described by Kemp, Harris and Calhoun. Brit. M. J., Dec. 22, 1906, and Am. J. Physiol., February, 1904.

10. Duke: J. A. M. A., 65:1600, 1916.

In Case 1, spectroscopic examinations were made with each count. Two bands of oxyhemoglobin were present at all times. In Case 8, the result was the same. In this case the blood looked dark, but this was not due to reduced hemoglobin. In Case 1 the blood never looked dark.

THE ATYPICAL CELLS

Atypical cells almost constantly appeared in the blood stream very soon after the injection of the foreign protein. They commonly continued throughout the reaction. They consisted largely of atypical large lymphocyte forms, and many small lymphocyte forms. In addition to these atypical cells, abnormal cell forms were frequently encountered, myelocytes, and nucleated reds both normoblasts and megaloblasts. Most of these forms are illustrated in the colored plates (Figs. 12 and 13). In Figure 12 Turck irritation forms, changes in the small lymphocyte group, are shown on the first and second lines. Granular, reticulated and multinucleated forms of the small lymphocyte group appear on lines three, four and five. Irregular nucleated and granular large lymphocytes are shown on lines six and seven and in Figure 13.

The Turck irritation forms are usually only found in pathologic blood, inflammatory processes, during or following a leukocytosis. They were only found preceding the first injection; that is, in the first control, before any foreign protein had been injected, in two cases (4 and 9). The former patient had an active gonorrhea, the latter a marked vulvovaginitis in which no gonococci could be found. Both of these patients were children. Four of these eight cases had previously had subcutaneous injections of so-called serum or vaccine. One had typhoid vaccination a year preceding the treatment. These findings would seem to show that an intravenous injection of typhoid protein initiates the appearance of Turck irritation forms.

Acidophil Granular Lymphocyte Forms.—These cells are frequently found in normal blood, but not in large numbers. We have noted two types of these cells. Those with very fine granules and those with large granules sometimes reaching the size of microcytes and not unlike them in appearance. The larger granular forms are the ones charted. Some of these cells show nuclei poor in chromatin and others have a vacuolated protoplasm. Many are binucleated and occasionally a mitotic form is seen. With one exception these forms were never encountered in the control. This patient showed 8 per cent. of the red granular forms in the control, and, in addition to this, there were many of the fine granular forms. The patient had recently been treated with vaccines preceding our investigation.

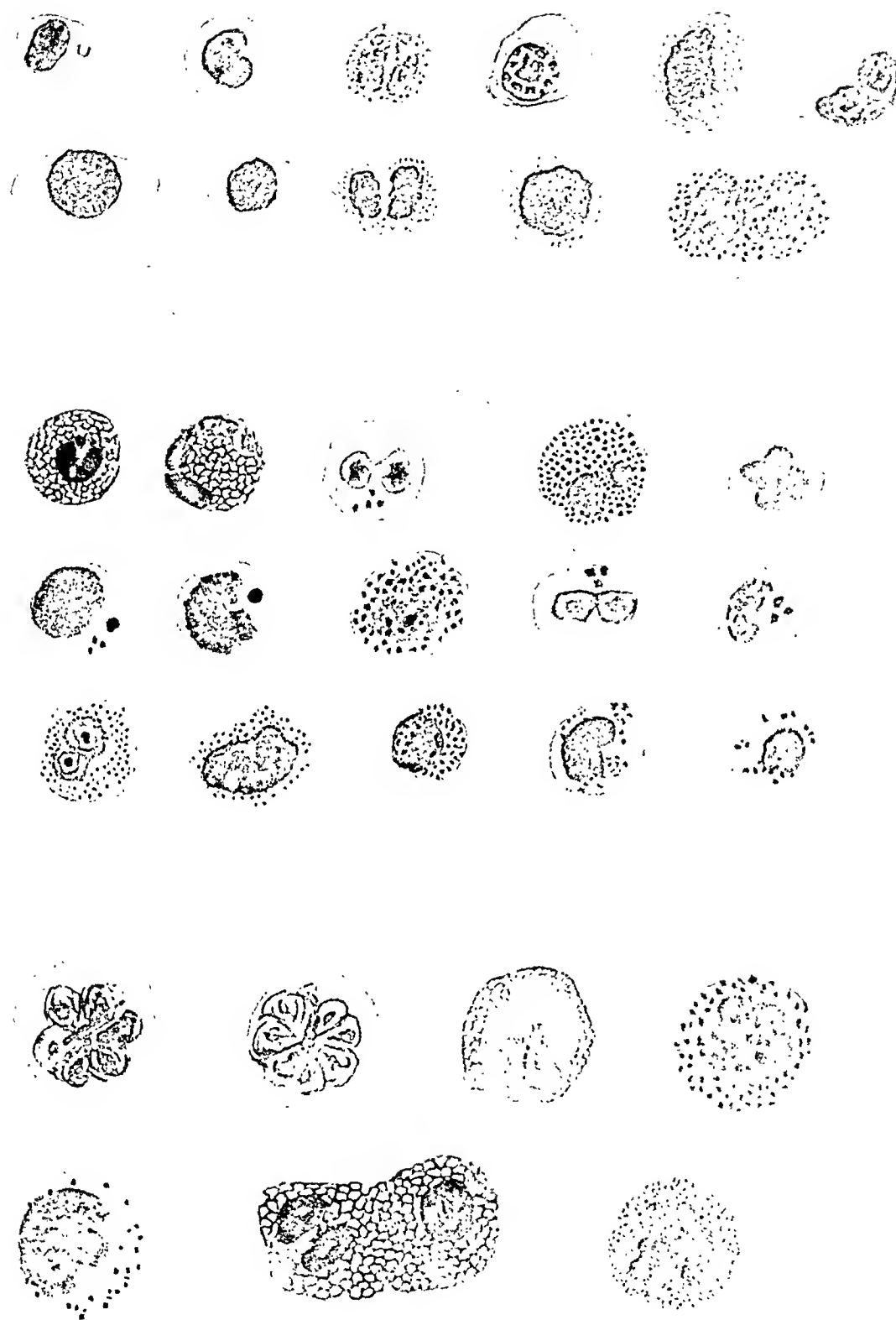


PLATE I
ATYPICAL WHITE BLOOD CORPUSCLE

ILLUSTRATING ARTICLE BY DAVID MURRAY COWIE, M.D., AND HENRIETTA CALHOUN, M.D.
ARCHIVES OF INTERNAL MEDICINE, JANUARY, 1919.

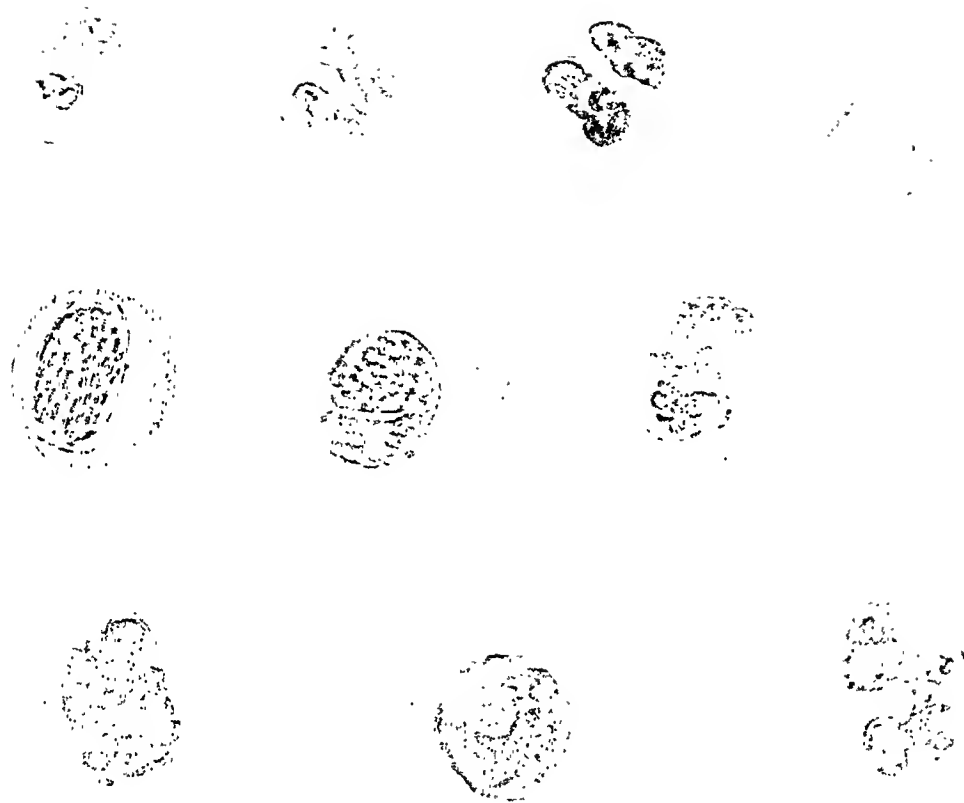


PLATE II
ATYPICAL LARGE LYMPHOCYTES—NONGRANULAR FORM

ILLUSTRATING ARTICLE BY DAVID MURRAY COWIE, M.D., AND HENRIETTA CALHOUN, M.D.
ARCHIVES OF INTERNAL MEDICINE, JANUARY, 1919.

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The significance of these cells has never been explained. Schleip remarks that they "are noted in every specimen" and have "no pathologic significance as yet." Their increase in numbers following the injection of typhoid protein would seem to indicate that they really are of pathologic significance.

The nature of the granules is not known. Being acidophil in reaction, their staining is akin to the particles found in eosinophilous cells and to erythrocytes, which are acidophil cells. These granules were also but seldom found in atypical large lymphocyte forms (last line, Fig. 12). Pepper and Miller¹¹ observed in one animal at the height of the leukocytosis following intravenous typhoid vaccine injection, "phagocytoses of erythrocytes" in smears from the peripheral blood. These phagocytic cells were large mononuclear cells. The same observation has been made in the blood of typhoid patients. So far as we know, the small lymphocyte has no phagocytic power either under normal or abnormal conditions. It seems improbable that these granules can be phagocytosed erythrocytes. They stain more brilliantly than do the erythrocytes around them. It seems to us that the red granule is due to some degenerative process or is present in response to some toxic substance.

The reticulated forms were found in the large and small lymphocyte groups. Not many were encountered. The reticulation was either basophil, acidophil or neutrophil. Examples of these cells are shown on lines three, six and seven, Figure 12.

The irregular small lymphocytes consisted of cells with rosette, cross-shaped, mitotic and bizarre formed nuclei. They were present in four out of seven controls and were distinctly more numerous after the intravenous injection. Small atypical forms were almost invariably the predominating cells where high atypical counts were shown.

When atypical large lymphocytes were found the percentage of typical large lymphocytes was always low, but there was no decrease from the preceding counts. The atypical large lymphocytes were almost always forms with a large pale nucleus taking a pale nuclear stain with the chromatin network well preserved. We have taken the ground that the transitional cell belongs in the small lymphocyte group and we do not care to enter any controversy over the possible relationship of the transitionals to these atypical cells. There is still no unanimity of opinion on the transitional question. Without exception, in the ten cases studied there was always an increase over the control in the number of the atypical large cells. We have regarded these as newly formed cells.

11. Pepper and Miller: J. Infect. Dis., 19: 1916.

DISCUSSION

The changes in the blood following the injection of a foreign protein (typhoid vaccine) are most remarkable. There is a sudden disappearance of the polymorphonuclear cells, which are soon replaced by an increase amounting in most cases to a hyperleukocytosis. Whether the disappearance is due to a destruction of cells or simply to their deposition in the tissues is not quite clear. The fact that we did not find an increase in the ordinary degenerating cells during the stage of leukopenia inclines us to the opinion that the leukopenia is due to migration. Then again, we are examining only peripheral blood and we have no knowledge of what has happened in the internal circulation. Pepper and Miller think that at least some of the leukocytes are destroyed. They could not find the usual accumulation of leukocytes in smears or tissue sections during the leukopenia stage.

When one watches from hour to hour the procession of cells into the blood stream during the stage of leukocytosis one is impressed with the newness of everything and with the idea that the whole affair is one of genesis. The polynuclears are young and the presence of myelocytes and of nucleated reds points to renewed activity of the respective mesenchymal tissues. Arneth counts made by Pepper and Miller during the leukocytosis showed a great increase in young forms.

The foreign protein seems to have stimulated all the mesenchymal tissues simultaneously. The order in which they are usually called on in infectious processes is, first, the neutrophil leukocytes without immature forms, second, metamyelocytes, third, myelocytes, fourth, promyelocytes, and fifth, megaloblasts (Photakes¹²).

The return of the leukocytes to normal, we believe, indicates that the increased production has ceased and that the excess of cells in the circulation is probably still passing into the tissues.

From these observations it will be seen that no matter what the pathologic condition is, injection of typhoid protein brings forth a similar reaction in all cases. The response differs only in degree. An important observation is that made from Case 3. We had no patient who reacted more violently in a pyrogenic way than this one; during the chill his bed would shake; his sweating was drenching and his pain was acute. He received ten injections, but never gave a leukocyte count above normal. This was a case of long standing. The leukocyte response grew less as the injections increased in number. On the other hand, a similar case, in a child (Case 1) of equally long standing reacted vigorously both pyrogenically and leukocytically. The result in this case was decidedly more marked and the patient still shows improvement two months after the treatment.

12. Photakes: *Deutsch. med. Wchnschr.*, Oct. 28, 1915.

The cases which showed the most improvement are 5, 8, 9, 10 and 1, all of which responded with marked leukocytosis, atypical cells and abnormal cells. All showed a marked myelocyte production and nucleated reds.

Cases 2 and 3 showed only slight myelocytic reaction. In the reactions (1, 2, 4) where myelocytes occurred in Case 3, the patient was very much better following the reactions. In the latter reactions no myelocytes were found, and he made very little if any improvement.

While nucleated red cells are present in most of the reactions where improvement was marked, they were also present in other cases.

An interesting observation is made in Case 4. This patient reacted with marked pyrogenic and leukocytic changes. The simplicity of the blood counts is remarkable. She showed no transitionals, no eosinophils, and in only one count were normal large lymphocytes present. Megalocytes occurred once in each of the two reactions studied; very few. No nucleated red cells were found. Atypical cells, though high at times, did not go far above the number in the control. These were almost entirely of the small lymphocyte type, atypical large cells being present in only three counts. These findings are of importance because of their association with a developmental absence of the epiphyses.

A CONSIDERATION OF THE ANALOGY BETWEEN THE TYPHOID PROTEIN PAROXYSM AND THE MALARIAL PAROXYSM

When we place side by side a series of temperature charts of typhoid protein reactions with the interval temperature curves between we have a very good picture of a case of simple tertian malaria. When we consider the mechanism at work producing the febrile reaction in each case we are still more impressed with their similarity. It is classic knowledge that the malarial paroxysm is associated with the birth of a new crop of young parasites, or due to it. We think there is every reason to warrant us in believing that the malarial paroxysm is a protein reaction due to the death of the parent cell, setting free in the blood stream a dose of dead malarial protein, and this brings about a group of symptoms analogous to or almost identical with that induced by the intravenous injection of typhoid protein.

In the reactions we have watched we note early slightly unpleasant feelings preceding slight chilliness, which frequently develops into a definite chill with rigor; then there is marked elevation of temperature, a general feeling by the patient of heat and a localized increase in the affected parts. This in turn is frequently followed by profuse sweating. The protein paroxysm lasts from eight to fifteen hours, when the patient again feels as well as before the reaction.

We are unable to find any record of consecutive or successive differential counts during a malarial paroxysm. At one time the absence of leukocytosis, with a rapidly rising temperature was con-

sidered "corroborative of malaria." A relative leukocytosis has been observed with a diminishing of the leukocytes toward the end of the reaction.

Krause⁷ reports a large number of differential counts on malaria patients. These counts were made at various times during a paroxysm on different patients, but no consecutive counts were made. He found a relative increase in the lymphocytes and a decrease in the polymorphonuclears, excepting from the beginning of the paroxysm up to about the fastigium or later, when there may be a decided absolute and relative increase in the polynuclears. He also noted at times a marked polymorphonuclear leukocytosis without the high fever; especially was this the case in an old infection. These findings fit in quite well with our findings during a protein paroxysm. It would be of great value to have a series of hourly counts during a malarial paroxysm.

The etiologic analogy between the two conditions is quite marked in the typhoid protein paroxysm. There is a billion dose of dead typhoid bacilli set free in the blood stream. It has been shown that in order to infect a mosquito the patient's blood must contain one crescent to every 500 leukocytes. It has also been shown that there may be from sixty-seven to ninety-two crescents per hundred leukocytes. A simple calculation will show that if this is the case, an ounce of blood might easily contain one billion malarial parasites; when these die the analogy is complete, a billion dose of dead malarial parasites has been set free in the blood stream and the typical reaction follows.

CONCLUSIONS

1. No matter what the condition is an intravenous injection of typhoid protein (vaccine) almost invariably initiates a leukopenia followed by a leukocytosis which is associated with, but not necessarily proportional to, the pyrogenic reaction.
2. The induced leukocytosis is chiefly polymorphonuclear even in those cases in which there is an initial lymphocyte increase.
3. A marked feature of the protein reaction is the appearance of atypical cell forms, particularly in the lymphocyte group; accompanying these there are nucleated reds and myelocytes.
4. We are inclined to the opinion that during the leukopenia stage the polynuclears leave the blood stream and enter the tissues, and that the subsequent increase in cells is due to an overproduction of cells from the respective mesenchymal fundaments, as is witnessed by the presence of myelocytes and nucleated reds. This view is further substantiated by the clinical findings of increased joint heat and swelling.

5. The temperature reaction and the clinical findings are not in the nature of an anaphylactic response, as is shown by the absence of an eosinophilia.

6. The cyanosis observed is not due to methemoglobin.

7. Improvement is most marked following those reactions in which there is a good myelocytic response. This is probably a measure of the capacity of the body to react.

8. The marked similarity between the typhoid protein paroxysm and the malarial paroxysm leads us to the belief that their production is due to a common etiologic factor — dead protein. The death of the malarial parasite sets free in the blood stream a sufficient amount of malarial protein to produce the typical protein reaction. The malarial paroxysm, therefore, is not due to the presence of the new organisms, as has been suggested, but to the death of the old ones.

We wish to acknowledge the kind assistance of Drs. Walthall, Beavin, and Kempton, members of the Pediatric Staff, in making leukocyte counts and clinical records.

The tables accompanying the article of Drs. Cowie and Calhoun will be found on the next and following pages.

TABLE 1.—CASE 1. FLORENCE S., AGED 11½ YEARS.—

—CHRONIC PLEURISY

Date and Hour	Total Leuko-cytes	Polys.	Eosin. Polys.	Baso. Polys.	Small Lymph.	Large Lymph.	Transi-tionals	Mast Cells	Myelo-cytes	Atyp- icals
11/16/17										
2:00 p. m.
Per cent.	100	54	0	0	31	13	2	0	0	0
Number	7,200	3,888	0	0	1,332	936	144	0	0	0
11/19/17										
First injection. Dose 500,000,000 T. V.										
12:15 p. m.
Per cent.	100
Number
1:15 p. m.
Per cent.	100	77½	0	0	20	2	½	0	0	0
Number	5,400	4,175	0	0	1,080	108	27	0	0	0
2:15 p. m.
Per cent.	100	75	1	0	20	2	0	0	0	2
Number	5,000	3,750	50	0	1,100	100	0	0	0	100
4:15 p. m.
Per cent.	100	88½	3½	0	4	8	½	0	0	
Number	11,400	9,089	398	0	456	342	57	0	0	57
11/22/17										
Second injection. Dose 1,000,000,000 T. V.										
1:30 p. m.
Per cent.	100	56	8	0	21½	16	8	0	0	1
Number	4,900	2,745	147	0	1,051	785	147	0	0	25
2:30 p. m.
Per cent.	100
Number
3:30 p. m.
Per cent.	100	61	1	0	29	6	1	0	0	2
Number	2,300	1,403	23	0	667	138	23	0	0	46
4:30 p. m.
Per cent.	100	88½	0	0	7	2½	1	0	½	½
Number	5,200	4,602	0	0	364	130	52	0	B 26	26
5:45 p. m.
Per cent.	100	89	1½	0	3	3½	½	0	0	1
Number	5,200	4,628	78	0	156	192	26	0	0	52
6:45 p. m.
Per cent.	100	89½	1	0	4	4	1	0	0	½
Number	5,600	4,812	56	0	224	224	56	0	0	26
8:00 p. m.
Per cent.	100	86	0	0	5	4	4	0	0	8
Number	14,500	13,470	0	0	725	580	580	0	0	435
9:00 p. m.
Per cent.	100	91	0	½	5	2	0	0	0	½
Number	15,900	14,469	0	80	795	318	0	0	0	79

CHRONIC POLYPERIARTHRITIS DEFORMANS

Leuko- cytes	Atypi- cals	Nucleated Reds	Plate- lets	Temper- ature	Pulse	Respi- ration	Spectro- scopic	Clinical
.....	0						
0	0							
0	0							
.....	98.4	84	..	Oxy. Hb.	Injected at 12:15
.....							
.....							
.....	1	100.4	Oxy. Hb.	1:05 p. m. chill
0	0							
0	0							
.....	4	102.2	84	..	Oxy. Hb.	Nauseated
0	2							
0	100							
.....	0	102.4	90	19	Oxy. Hb.	Free movement
0	1/2							
0	57							
.....	0	99.0	78	20	Oxy. Hb.	Injected at 1:30 p. m.
0	1/2							
0	25							
.....	102.4	80	20	Oxy. Hb.	2:00 p. m. chill lasting 45 minutes
.....							
.....							
.....	2		103.0	80	23	Oxy. Hb.	
0	2							
0	40							
.....	0	104.3	82	22	Oxy. Hb.	Nauseated; pain in back
1/2	1/2							
B 26	26							
.....	0	103.0	98	32	Oxy. Hb.	
0	1							
0	52							
.....	0	102.0	88	24	Oxy. Hb.	
0	1/2							
0	28							
.....	0	102.2	98	36	Oxy. Hb.	Pain in back
0	3							
0	485							
.....	0	102.2	88	32		
0	1/2							
0	79							

TABLE 1.—CASE 1. FLORENCE S., AGED 11½ YEARS.—

—CHRONIC POLYPT

Date and Hour	Total Leuko-cytes	Polys.	Eosin. Polys.	Baso. Polys.	Small Lymph.	Large Lymph.	Transl-tionals	Mast Cells	Myelo-cytes	Atyp-icals
11/23/17										
7:00 p. m.
Per cent.	100	88½	1	0	6	3½	1	0	0	0
Number	12,800	10,328	128	0	768	448	128	0	0	0
11/25/17										
Third injection. Dose 1,000,000,000 T. V.										
9:30 a. m.
Per cent.	100
Number
10:30 a. m.
Per cent.	100	47	0	0	37	20	4	0	2	0
Number	2,000	940	0	0	740	400	80	0	40	0
12 noon.....
Per cent.	100	73	4	0	10	6	1	0	0	6
Number	4,000	2,920	160	0	400	240	40	0	0	240
1:00 p. m.
Per cent.	100	83	3	0	3	4	1	1	3	2
Number	5,100	4,233	153	0	153	204	51	51	B 153	102
2:00 p. m.
Per cent.	100	83½	3	½	5	6	1	0	1½	½
Number	5,200	4,342	156	26	260	312	52	0	B 73	26
3:00 p. m.
Per cent.	100	84	3	0	5	5	2	0	1	0
Number	5,600	4,707	163	0	280	280	112	0	B 56	0
4:30 p. m.
Per cent.	100	93	½	0	5	½	0	0	0	1
Number	27,600	25,688	138	0	1,380	138	0	0	0	276
6:00 p. m.
Per cent.	100	80	2	0	12	3	1	½	½	1
Number	19,500	15,600	390	0	2,340	535	195	98	B 97	195
7:30 p. m.
Per cent.	100	91	½	0	5½	2	½	0	0	½
Number	16,000	14,560	80	0	640	320	80	0	0	80
11/26/17										
11:00 a. m.
Per cent.	100	55½	1½	0	26	9½	3	0	2	2½
Number	10,800	9,990	1,620	0	2,808	1,026	324	0	B 216	470
11/29/17										
9:00 a. m.
Per cent.	100	68	5		15½	6½	2	1	0	2
Number	6,100	4,148	305		945	397	122	61	0	122

Leuko- cytes	Atypi- cals	Nucleated Reds	Plate- lets	T
.....	0	
0	0			
0	0			
.....	
.....			
.....			
.....	0	
2	0			
40	0			
.....	0	
0	6			
0	240			
.....	0	
3	2			
B 153	102			
.....	0	
1½	½			
B 78	26			
.....	0	
1	0			
B 56	0			
.....	0	
0	1			
0	276			
.....	0	
½	1			
B 97	195			
.....	0	
0	½			
0	80			
.....	0	
2	2½			
B 216	270			
.....	0	
0	2			
0	122			

					Nucle-	Tem- per-	Pulse Res
TABLE 2.—CASE 4.	MRS. W., AGED 57.	CHRONIC TERMIATILIS,	NO STRUCTURAL CHANGE	9.			

[illegible]

[illegible]

TABLE 3.—CASE 3. BLAIS, AGED 59. CHRONIC INFECTIOUS POLYPERIARTHRITIS DEFORMANS—(Continued)

Date and Hour	Total Leukocytes	Polys.	Eosin. Polys.	Baso. Polys.	Small Lymph.	Large Lymph.	Transi- tionals	Mast Cells	Myelo- cytes	Atypi- cals	Nucle- ated Reds	Plate- lets	Tem- per- ature	Pulse	Respi- ration	Clinical
2/10/18 Fifth injection Dose 1,000,000,000 T. V.																
11 a. m.	100	58½	0	0	34	½	0	0	½	6½	0	...	98.6	90	20	Injected at 10:30 a. m.
Per cent.	6,700	3,920	0	0	2,278	33	0	0	33	436						
Number.....																
12 noon.....	100	62	0	½	28½	1	½	0	0	7½	0	...	100.0	92	22	Chill lasting 25 minutes
Per cent.	4,500	2,790	0	22	1,283	45	22	0	0	338						
Number.....																
1 p. m.	100	85	0	0	15	0	0	0	0	0	0	...	101.0	100	22	
Per cent.	5,800	4,930	0	0	870	0	0	0	0	0						
Number.....																
3 p. m.	100	88½	0	0	11½	0	0	0	0	0	0	...	103.0	112	22	
Per cent.	6,900	6,107	0	0	703	0	0	0	0	0						
Number.....																
5 p. m.	100	87	0	0	10½	½	0	0	0	2	0	...	101.0	120	22	
Per cent.	7,700	6,699	0	0	869	38	0	0	0	154						
Number.....																
7:30 p. m.	100	91½	0	0	7½	0	0	0	0	1	0	...	100.0	114	22	
Per cent.	6,800	6,222	0	0	510	0	0	0	0	68						
Number.....																
2/13/18 Sixth injection Dose 1,000,000,000 T. V.																
10:30 a. m.	100	70	0	0	29	0	0	0	0	1	0	...	100.2	100	22	Injected at 10:30 a. m.
Per cent.	6,600	4,520	0	0	1,914	0	0	0	0	63						
Number.....																
12:30 p. m.	100	70	0	0	25	½	½	0	0	2½	0	...	100.2	98	20	
Per cent.	4,100	2,870	0	0	1,025	20	21	0	0	103						
Number.....																

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10:15 a. m.	100	71	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0</
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TABLE 5.—CASE 5. MISS W., AGED 22. ACUTE RHEUMATISM, JOINT SWELLING—NO STRUCTURAL CHANGE

Date and Hour	Total Leuko-cytes	Polys.	Eosin. Polys.	Baso. Polys.	Small Lymph.	Large Lymph.	Transi-tionals	Mast Cells	Myelo-cytes	Atypi-cals	Nucle-ated Reds	Plate-lets	Tem-pera-ture	Pulse	Respi-ration	Olinical
12/28/17																
Control counts																
11 a. m.	100	62	1/2	0	29	5	3 1/2	0	0	0	0					
Per cent.	20,000	12,400	100	0	5,800	1,000	700	0	0	0	0					
Number.....																
12 a. m.	100	60	1/2	1/2	31	2 1/2	2	0	0	1/2	0					
Per cent.	18,800	11,280	94	94	6,392	470	376	0	0	94	0					
Number.....																
1 p. m.	100	70 1/2	0	0	23 1/2	4 1/2	1 1/2	0	0	0	0					
Per cent.	22,100	15,681	0	0	5,194	991	331	0	0	0	0					
Number.....																
2 p. m.	100	67	0	1/2	27	3 1/2	1 1/2	0	0	1/2	0					
Per cent.	15,800	10,586	0	79	4,263	553	237	0	0	79	0					
Number.....																
3 p. m.	100	69 1/2	1/2	1/2	22	2	2	0	1 1/2	3	0					
Per cent.	22,800	15,840	114	114	5,016	456	456	0	N 114	648	0					
Number.....																
4 p. m.	100	66	1/2	0	28	2 1/2	0	1/2	1 1/2	2	0					
Per cent.	17,600	11,616	88	0	4,928	440	0	88	N 204	352	0					
Number.....																
5 p. m.	100	74	0	0	22	2	1	1/2	0	1 1/2	0					
Per cent.	17,300	12,802	0	0	3,406	340	173	87	0	259	0					
Number.....																
6 p. m.	100	70 1/2	0	0	26	0	1/2	0	0	3	0					
Per cent.	18,100	11,760	0	0	4,706	0	91	0	0	543	0					
Number.....																
12/29/17																
First injection																
Dose 1,000,000,000																
T. V.																
8 a. m.	100	68 1/2	0	0	28 1/2	1	1 1/2	0	0	1/2	0					
Per cent.	21,600	14,796	0	0	6,166	216	324	0	0	108	0					
Number.....																Injected at 8 a. m.

8:30 a. m. 100 ... 1/2 ... 0 ... 84 ... 20
Per cent. 13,300 ... 0 ... 0 ... 0 ... 0 ...
Number..... 13,300 ... 0 ... 0 ... 0 ... 0 ...
9 a. m. 100 ... 1/2 ... 0 ... 0 ... 0 ...

[illegible]

	11 a. m.	12 noon.	1 p. m.	2 p. m.	3 p. m.	4 p. m.	5 p. m.	6 p. m.	7 p. m.	8 p. m.	1/18/18 Third Injection Dose 1,000,000,000 T. V.	1 p. m.	1:30 p. m.
Per cent.	100	100	100	100	100	100	100	100	100	100	100	100	100
Number	2,600	4,500	7,600	6,500	5,300	6,000	6,000	5,300	5,900	4,300	10,000	10,000	10,300
Per cent.	71	83	82	92 1/2	84	92 1/2	76 1/2	68 1/2	64	63 1/2	55	55	41
Number	1,846	3,735	6,232	6,013	4,452	6,013	5,049	3,631	3,776	2,731	5,500	5,500	4,223
Per cent.	1	7	16	6	13 1/2	18	18	27	28 1/2	32	39 1/2	39 1/2	56
Number	494	315	1,216	390	716	1,158	1,158	1,431	1,631	1,375	3,950	3,950	5,703
Per cent.	2	4	1	1	0	2 1/2	2 1/2	0	2	1/2	3	3	1
Number	52	180	76	65	0	165	99	0	118	26	800	800	103
Per cent.	0	3	0	0	0	1 1/2	1 1/2	1 1/2	2	0	1 1/2	1 1/2	1
Number	0	135	0	0	0	0	27	0	0	0	150	150	103
Per cent.	0	0	0	0	0	0	0	0	0	0	0	0	0
Number	0	45	0	0	0	0	0	0	0	0	0	0	0
Per cent.	1	0	0	0	0	0	0	1/2	30	0	0	0	0
Number	26	0	0	0	0	0	0	27	0	0	0	0	0
Per cent.	6	2	1	37	120	99	186	177	4	172	50	50	0
Number	216	90	76	0	120	0	0	0	0	0	0	0	0
Per cent.	102.2	100.9	102.3	102.4	102.6	103.2	103.6	103.2	102.0	98.8	98.8	98.8	98.8
Number	116	88	100	96	100	96	108	108	88	92	92	92	98
Per cent.	24	26	24	24	24	20	24	22	20	22	22	22	20
Number	24	26	24	24	24	20	24	22	20	22	22	22	20

TABLE 5.—CASE 5. MISS W., AGED 22. ACUTE RHEUMATISM, JOINT SWELLING—No STRUCTURAL CHANGE—(Continued)

Date and Hour	Total Leuko-cytes	Polys.	Eosin. Polys.	Baso. Polys.	Small Lymph.	Large Lymph.	Transl. tionals	Mast Cells	Myelo-cytes	Atyp- icals	Nucle- ated Reds	Plate- lets	Tem- per- ature	Pulse	Respi- ration	Clinical
2 p. m.	100	63	0	0	29	1 1/2	1 1/2	0	0	0	0	...	98.8	98	20	Severe chill lasting from 2:30-3:10
Per cent.	9,900	6,534	0	0	2,871	1,465	1,405	0	0	198	0	...				
Number.....																
2:30 p. m.	100	59	0	0	34	6	1	0	0	0	0	...	99.0	100	22	
Per cent.	8,500	5,015	0	0	2,890	510	83	0	0	0	0	...				
Number.....																
3 p. m.	100	73 1/2	0	0	26 1/2	0	0	0	0	0	0	...	100.2	102	22	Still complains of cold; nauseated
Per cent.	6,200	4,557	0	0	1,643	0	0	0	0	0	0	...				
Number.....																
4:30 p. m.	100	76 1/2	0	0	21	1	1	0	0	1/2	0	...	102.2	124	24	
Per cent.	4,100	3,360	0	0	924	44	41	0	0	22	0	...				
Number.....																
5 p. m.	100	72	0	0	17	3	3	0	0	0	0	...	101.8	124	22	
Per cent.	5,400	3,788	0	0	918	162	162	0	0	0	0	...				
Number.....																
6 p. m.	100	86	0	0	11	2	1	0	0	0	0	...	102.6	120	24	
Per cent.	10,500	9,030	0	0	1,155	210	105	0	0	0	0	...				
Number.....																
7 p. m.	100	92 1/2	0	0	2 1/2	1 1/2	2 1/2	0	1/2	1/2	0	...	102.4	120	24	
Per cent.	13,600	12,580	0	0	336	200	336	0	N 68	68	0	...				
Number.....																
8 p. m.	100	91 1/2	0	1/2	4	1 1/2	2	0	0	1/2	0	...	101.8	116	24	
Per cent.	20,400	18,666	0	102	810	306	408	0	0	102	0	...				
Number.....																
9 p. m.	100	90	0	0	6 1/2	1 1/2	1 1/2	0	0	1/2	0	...	101.0	108	24	
Per cent.	11,400	10,360	0	0	641	171	171	0	0	57	0	...				
Number.....																
10 p. m.	100	87	0	0	5 1/2	2 1/2	4	0	1/2	1/2	0	...	101.0	102	22	
Per cent.	15,100	13,137	0	0	880	378	604	0	N 76	75	0	...				
Number.....																
11 p. m.	100	100.8	96	22	
Per cent.				
12 Per cent.	100	100.0	92	22	

TABLE 6.—CASE 6. MISS WOR., AGED 22. HYPERTROPHIC ARTHRITIS.

Date and Hour	Total Leuko-cytes	Polys.	Eosin. Polys.	Baso. Polys.	Small Lymph.	Large Lymph.	Transl. tionals	Mast Cells	Myelo-cytes	Atyp- icals	Nucle- ated	Plate- lets	Tem- per- ature	Pulse	Respi- ration	Clinical
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WOMAN AGED 22. HYPERTROPHIC ARTHRITIS

[illegible]

[illegible]

[illegible]

TABLE 8.—CASE 8. MRS. B., AGED 46. HYPERTROPHIC ARTHRITIS OF SPINE—(Continued)

Date and Hour	Total Leuko-cytes	Polys.	Eosin. Polys.	Baso. Polys.	Small Lymph.	Large Lymph.	Transl-tionals	Mast Cells	Myelo-cytes	Atypi-cals	Nucle-ated Reds	Plate-lets	Tem-pera-ture	Pulse	Respi-ration	Clinical
9:10 a. m. Per cent. Number.....	100 2,450	17 417	0 0	1/2 12	70 1,715	3 74	0 0	0 0	4 N. 98	5 1/2 134	0	...	99.5	75	20	
9:40 a. m. Per cent. Number.....	100 5,350	50 1/2 2,702	0 0	1/2 26	39 2,087	2 1/2 123	2 107	1 25	2 N. 107	2 1/2 123	1	...	100.2	108	30	Headache
10:10 a. m. Per cent. Number.....	100 9,150	77 1/2 7,092	0 0	0 0	22 1/2 2,058	0 0	0 0	0 0	0 0	0 0	0	...	101.2	108	24	
11:10 a. m. Per cent. Number.....	100 7,400	93 6,882	0 0	0 0	7 518	0 0	0 0	0 0	0 0	0 0	0	...	101.2	93	23	
12:10 p. m. Per cent. Number.....	100 14,500	87 1/2 12,667	0 0	1/2 73	11 1,595	0 0	0 0	0 0	1/2 B. 72	1/2 73	0	...	100.6	88	26	
2:10 p. m. Per cent. Number.....	100 13,300	80 14,640	0 0	0 0	18 1/2 3,385	1/2 92	0 0	0 0	0 0	1 183	0	...	100.0	90	26	
3:10 p. m. Per cent. Number.....	100 10,500	80 1/2 13,282	1/2 83	0 0	16 2,640	2 330	1 165	0 0	0 0	0 0	0					
4:10 p. m. Per cent. Number.....	100 9,450	77 7,276	0 0	0 0	14 1,323	3 284	4 1/2 425	0 0	0 0	1 1/2 142	0	Large saus- age shap'd	100.0	80	22	
5:10 p. m. Per cent. Number.....	100 10,000	77 1/2 7,750	0 0	0 0	15 1,500	2 200	4 1/2 450	0 0	1/2 50	1/2 50	0	...	100.0	80	24	Comfortable
2/12/18 2 p. m. Per cent. Number.....	100 5,550	47 2,608	1 1/2 83	1/2 28	37 1/2 2,081	6 1/2 361	2 1/2 134	1/2 28	2 1/2 N. & B. 134	1 1/2 83	0	...	98.8	78	21	
2/13/18 Third injection Dose 1,000,000,000 I. V. Per cent. Number.....	100 7,150	64 4,576	1/2 36	1 71	18 1,287	10 715	4 266	0 0	0 0	2 1/2 179	0	...	98.4	80	20	Injected at 8:15 a. m.

8:55 a. m. Per cent. Number.....	100 4,250	50 1/2 2,401	0 0	1/2 21	37 1,573	2 1/2 21	1/2 21	0 0	1 1/2 B. 61	3 1/2 140	0	...	98.4	75	20	8:30, chill lasting 25 minutes
9:25 a. m. Per cent. Number.....	100 4,250	18 18	0	...	99.5	91	20	

[illegible]

TABLE 9.—CASE 9. FRANCES C., AGED 2. GONORRHEAL VULVOVAGINITIS

Date and Hour	Total Leuko-cytes	Polys.	Eosin. Polys.	Baso. Polys.	Small Lymph.	Large Lymph.	Transl. tionals	Mast Cells	Myelo-cytes	Atyp- icals	Nucle- ated Reds	Plate- lets	Tem- per- ature	Pulse	Respi- ration	Clinical
1/8/18. Control 4 p. m. Number.....	10,900															
6 p. m. Number.....	12,300															
7 p. m. Number.....	12,800															
8 p. m. Per cent.	100	49	0	0	48	1/2	0	0	0	2 1/2	0					
Number.....	11,400	5,586	0	0	5,472	57	0	0	0	282						
1/9/18 First injection Dose 1,000,000,000 T. V.																
6 a. m. Per cent.	100	63 1/2	0	0	20 1/2	3	0	0	0	4	0		99.1	104	24	Injected at 8 a. m.
Number.....	11,200	6,112	0	0	3,304	336	0	0	0	448						
8:30 a. m. Per cent.	100	61 1/2	1 1/2	0	20 1/2	1 1/2	5	0	1	2	0		99.8	124	24	
Number.....	7,800	4,797	39	0	2,301	39	390	0	B. 78	156						
9 a. m. Per cent.	100	52 1/2	1 1/2	1/2	40	1 1/2	1	0	0	2 1/2	0		99.4	84	28	
Number.....	6,300	3,308	100	37	2,520	100	63	0	B. 37	164						
9:30 a. m. Per cent.	100	57	1	0	34	2	1	0	0	5	0		99.8	88	28	
Number.....	7,100	4,047	71	0	2,414	142	71	0	0	355						
10 a. m. Per cent.	100	62 1/2	0	0	34 1/2	1/2	0	0	0	2	0		100.2	102	26	
Number.....	7,800	4,095	0	0	2,601	39	0	0	B. 39	156						
11 a. m. Per cent.	100	64 1/2	1/2	1/2	26 1/2	2 1/2	1/2	0	0	4 1/2	0		100.2	112	28	
Number.....	11,300	7,289	56	56	2,965	283	56	0	B. 56	503						
12 noon. Per cent.	100	75	0	0	18	2	1 1/2	0	0	2 1/2	0		100.4	98	26	
Number.....	12,000	9,000	0	0	2,160	240	180	0	B. 120	300						
1 p. m. Per cent.	100	70	0	0	15 1/2	2 1/2	1	0	0	2	0		100.4	120	28	
Number.....	28,000	22,120	0	0	4,340	700	280	0	0	500						

2 p. m. Per cent.	100	78	0	0	13 1/2	1 1/2	1/2	0	0	3	0		100.7	128	30	
Number.....	18,000	14,040	0	0	2,370	270	90	0	B. 90	540						
3 p. m. Per cent.	100	74	0	0	18	0	2	0	0	6	0		100.5	124	32	
Number.....	10,600	7,744	0	0	1,908	0	212	0	0	636						
4 p. m. Per cent.	100	74	0	0	18	0	2	0	0	6	0		100.5	100	30	
Number.....	10,600	7,744	0	0	1,908	0	212	0	0	636						

2 p. m.	100	78	0	0	10 1/2	1 1/2	90	0	0	1/2	0	0	...	0	...	100.7	128	36
Per cent.	18,000	14,040	0	0	2,970	270	0	0	0	0	0	0	...	0	...	100.5	124	32
Number.....	100	74	0	0	18	0	212	0	0	0	0	0	...	0	...	100.5	100	36
3 p. m.	100	7,744	0	0	1,908	0	0	0	0	0	0	0	...	0	...	100.8	120	36
Per cent.	10,600	7,744	0	0	1,100	0	110	0	0	0	0	0	...	0	...	100.8	120	36
Number.....	100	87	0	0	10	0	1	0	0	0	0	0	...	0	...	100.8	120	36
4 p. m.	100	9,750	0	0	1,100	0	110	0	0	0	0	0	...	0	...	100.8	120	36
Per cent.	11,000	9,750	0	0	44	109	54	0	0	0	0	0	...	0	...	100.8	120	36
Number.....	100	50 1/2	0	0	4,796	1	109	0	0	0	0	0	...	0	...	100.8	120	36
5 p. m.	100	5,505	0	0	27	1	0	0	0	0	0	0	...	0	...	100.8	120	36
Per cent.	10,900	5,505	0	0	2,943	109	0	0	0	0	0	0	...	0	...	100.8	120	36
Number.....	100	64	0	0	0	0	0	0	0	0	0	0	...	0	...	100.8	120	36
1/10/18	100	6,976	0	0	0	0	0	0	0	0	0	0	...	0	...	100.8	120	36
4:30 p. m.	100	64	0	0	2,943	109	0	0	0	0	0	0	...	0	...	100.8	120	36
Per cent.	10,900	6,976	0	0	0	0	0	0	0	0	0	0	...	0	...	100.8	120	36
Number.....	100	64	0	0	0	0	0	0	0	0	0	0	...	0	...	100.8	120	36
1/12/18	100	64	0	0	0	0	0	0	0	0	0	0	...	0	...	100.8	120	36
Second Injection	100	64	0	0	0	0	0	0	0	0	0	0	...	0	...	100.8	120	36
Dose 1,000,000,000	100	64	0	0	0	0	0	0	0	0	0	0	...	0	...	100.8	120	36
T. V.	100	64	0	0	0	0	0	0	0	0	0	0	...	0	...	100.8	120	36
9:30 a. m.	100	57	1	113	34	226	226	2	0	0	0	0	...	0	...	100.8	120	36
Per cent.	11,300	6,441	1	113	3,812	226	226	2	0	0	0	0	...	0	...	100.8	120	36
Number.....	100	43	6	456	47	152	76	1	0	0	0	0	...	0	...	100.8	120	36
10 a. m.	100	3,268	6	456	3,572	152	76	1	0	0	0	0	...	0	...	100.8	120	36
Per cent.	7,600	3,268	6	456	3,572	152	76	1	0	0	0	0	...	0	...	100.8	120	36
Number.....	100	50	2	166	37	332	166	2	0	0	0	0	...	0	...	100.8	120	36
10:30 a. m.	100	4,150	2	166	3,071	332	166	2	0	0	0	0	...	0	...	100.8	120	36
Per cent.	8,300	4,150	2	166	3,071	332	166	2	0	0	0	0	...	0	...	100.8	120	36
Number.....	100	61	1	81	30 1/2	446	51 1/2	1	0	0	0	0	...	0	...	100.8	120	36
11 a. m.	100	4,941	1	81	2,470	446	51 1/2	1	0	0	0	0	...	0	...	100.8	120	36
Per cent.	8,100	4,941	1	81	2,470	446	51 1/2	1	0	0	0	0	...	0	...	100.8	120	36
Number.....	100	62	0	0	30	184	2	184	0	0	0	0	...	0	...	100.8	120	36
11:30 a. m.	100	5,604	0	0	2,760	184	2	184	0	0	0	0	...	0	...	100.8	120	36
Per cent.	9,200	5,604	0	0	2,760	184	2	184	0	0	0	0	...	0	...	100.8	120	36
Number.....	100	60	0	0	40	0	0	0	0	0	0	0	...	0	...	100.8	120	36
12 noon.....	100	5,520	0	0	3,060	0	0	0	0	0	0	0	...	0	...	100.8	120	36
Per cent.	9,200	5,520	0	0	3,060	0	0	0	0	0	0	0	...	0	...	100.8	120	36
Number.....	100	64	0	0	30	405	3	405	0	0	0	0	...	0	...	100.8	120	36
1 p. m.	100	8,640	0	0	4,050	405	3	405	0	0	0	0	...	0	...	100.8	120	36
Per cent.	13,500	8,640	0	0	4,050	405	3	405	0	0	0	0	...	0	...	100.8	120	36
Number.....	100	65	1	160	31	320	2	0	0	0	0	0	...	0	...	100.8	120	36
2 p. m.	100	10,500	1	160	4,960	320	2	0	0	0	0	0	...	0	...	100.8	120	36
Per cent.	16,000	10,500	1	160	4,960	320	2	0	0	0	0	0	...	0	...	100.8	120	36
Number.....	100	65	1	160	31	320	2	0	0	0	0	0	...	0	...	100.8	120	36

Injected at 9:30 a. m.

TABLE 9.—CASE 9. FRANCES C., AGED 2. GONORRHEAL VULVOVAGINITIS—(Continued)

Date and Hour	Total Leuko-cytes	Polys.	Eosin. Polys.	Baso. Polys.	Small Lymph.	Large Lymph.	Transi-tionals	Mast Cells	Mycelo-cytes	Atyp-i-cals	Nucle-ated Reds	Plate-lets	Tem-pera-ture	Pulse	Respi-ration	Clinical
3 p. m.
Per cent.
Number.....	13,400	8,710	0	0	3,350	536	268	0	0	536	0	...	100.0	104	36	
4 p. m.
Per cent.
Number.....	13,500	9,690	135	0	2,565	135	135	0	0	540	0	...	100.2	120	30	
5 p. m.
Per cent.
Number.....	13,400	9,782	0	0	2,144	804	268	0	B. 134	268	0	...	100.4	112	32	
6 p. m.
Per cent.
Number.....	13,500	9,990	0	0	2,970	270	270	0	0	135	0	...	100.4	112	32	
7 p. m.
Per cent.
Number.....	11,900	9,163	0	0	2,261	119	119	0	0	238	1	...	99.9	108	32	
1/25/18																
Third injection																
10:30 a. m.
Per cent.
Number.....	12,000	7,920	120	0	3,000	0	0	0	0	960	3	...	99.5	92	24	Injected at 10:25 a. m.
12:30 p. m.
Per cent.
Number.....	7,200	4,464	0	0	1,914	144	216	0	B. 72	360	0	...	101.0	132	36	
2:30 p. m.
Per cent.
Number.....	9,400	7,238	0	0	940	282	564	0	0	366	0	...	102.2	128	38	
5:30 p. m.
Per cent.
Number.....	36,900	28,782	369	0	1,476	369	2,723	0	0	3,321	2	...	101.0	120	28	
8:30 p. m.
Per cent.
Number.....	11,300	8,475	0	0	1,130	226	113	0	B. & N. 339	1,017	3	...	101.0	128	28	

Injected 11:40 a.m.																	
1/28/18	Fourth injection	100	69 1/2	1	1	25	1	1	0	117	1	117	0	...	99.1	86	24
	11:40 a.m.	11,700	8,132	117	117	2,925	117	117	0	58	...	176	0	...	101.0	136	34
	Per cent.											...					
	Number											...					
1:30 p.m.		100	66	2	2	27	2	61	0	2	...	100.6	120	32
	Per cent.	6,100	4,026	122	122	1,647	122	...	0	0
	Number										
4 p.m.		100	74	0	0	10	1	768	0	0	...	99.6	112	28
	Per cent.	12,800	9,472	0	0	1,280	128	...	0	0
	Number										
6:30 p.m.		100	86	0	0	9	1	156	0	0	...	99.2	104	22
	Per cent.	15,600	13,416	0	0	1,404	156	...	0	0
	Number										
8:30 p.m.		100	80	0	0	19	1	0	0	0	...	98.6	98	20
	Per cent.	21,200	16,960	0	0	4,028	212	...	0	0
	Number										
10:30 p.m.		100	88	0	0	16	0	153	0	0	...	100.8	116	30
	Per cent.	15,300	12,699	0	0	2,448	0	...	0	0
	Number										
2/1/18	Fifth injection	100	63	1	2	31	2	219	0	0	...	101.0	106	26
	3 p.m.	7,300	4,597	73	146	2,263	146	...	0	0
	Per cent.										
	Number										
5 p.m.		100	75	0	2	10	2	72	0	0	...	101.0	92	20
	Per cent.	7,200	5,400	0	144	720	144	...	0	0
	Number										
7 p.m.		100	75	0	3	22	3	0	0	0
	Per cent.	12,400	9,300	0	372	2,728	372	...	0	0
	Number										
2/17/18		100	38	0	1 1/2	56	1 1/2	82	0	0
	9:15 a.m.	8,200	3,116	0	99	4,592	99	...	0	0
	Per cent.										
	Number										

[illegible]

TABLE 10.—CASE 10. FREI., AGED 9. SUPPURATIVE MASTOIDITIS WITH CHRONIC PULMONARY TUBERCULOSIS—(Continued)

[illegible][illegible]

Chill for 15 min.																
8:30 a. m.	100	53	0	1/2	42	2	1	1/2	1	21	0	0	0	99.2	132	24
Per cent.	4,100	2,173	0	0	881	82	41	0	0	0	0	0	0	...	132	32
Number
9 a. m.	100	60	0	0	38	1/2	31	0	0	0	0	0	0	99.6	132	32
Per cent.	6,100	3,660	0	0	2,318	30	0	0	0	0	0	0	0	...	132	...
Number
9:30 a. m.	100	62	0	0	36	0	80	0	0	0	0	0	0	102.0	164	32
Per cent.	15,900	9,858	0	0	5,724	0	0	0	0	0	0	0	0	...	164	...
Number
10 a. m.	100	93	0	0	51/2	197	1/2	0	0	0	0	0	0	102.2	160	32
Per cent.	39,300	39,549	0	0	2,161	197	1/2	0	0	0	0	0	0	...	160	...
Number
10:30 a. m.	100	89	0	0	9	0	0	0	0	0	0	0	0	99.2	132	28
Per cent.	31,600	28,124	0	0	2,844	0	0	0	0	0	0	0	0	...	132	...
Number
11:30 a. m.	100	93	0	0	2	296	1	0	0	0	0	0	1	98.4	132	24
Per cent.	29,600	27,528	0	0	592	296	296	180	1/2	0	0	0	0	...	132	...
Number
12:30 p. m.	100	91	0	180	6	181	1/2	0	0	0	0	0	0	98.4	132	24
Per cent.	36,100	32,851	0	0	2,166	181	1/2	0	0	0	0	0	0	...	132	...
Number
1:30 p. m.	100	80	0	0	14	174	1/2	0	0	0	0	0	0	98.7	120	24
Per cent.	34,800	27,840	0	0	4,872	174	1/2	0	0	0	0	0	0	...	120	...
Number
2:30 p. m.	100	86	165	1/2	101/2	165	1/2	166	1/2	0	0	0	0	98.5	124	26
Per cent.	33,100	28,406	165	0	3,476	165	1/2	166	1/2	0	0	0	0	...	124	...
Number
3:30 p. m.	100	84	0	0	13	268	1	134	1/2	0	0	0	1	98.3	124	24
Per cent.	26,800	22,512	0	0	3,484	268	1	134	1/2	0	0	0	0	...	124	...
Number
4:30 p. m.	100	80	0	0	15	360	1/2	120	1/2	0	0	0	0	98.4	120	24
Per cent.	24,000	19,200	0	0	3,600	360	1/2	120	1/2	0	0	0	0	...	120	...
Number
5:30 p. m.	100	76 1/2	112	1/2	18	450	2	225	1	113	1/2	112	0	98.8	128	24
Per cent.	22,500	17,213	112	0	4,050	450	2	225	1	113	1/2	112	0	...	128	...
Number
6:30 p. m.	100	82	0	1/2	11 1/2	2,530	11 1/2	21/2	1	110	1/2	110	0
Per cent.	22,000	18,040	0	0	2,530	2,530	11 1/2	21/2	1	110	1/2	110	0
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THE CAUSE OF THE REACTIONS FOLLOWING TRANSFUSION OF CITRATED BLOOD *

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AND

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In analyzing the reactions following blood transfusion by any of the different methods now in vogue, all figures should be based on cases in which donor and recipient have been properly matched prior to the operation. By means of the methods for grouping and direct matching given us by Moss¹ and others it is possible to exclude a certain number of gross hemolytic reactions which used to be inevitable. It is also a very simple matter to list a number of Group 4 donors, and with this done no emergency transfusion need ever become a completely reckless venture. In our experience it would appear possible to use carefully classified Group 4 donors for all cases, relying on the fact that the high dilution to which the incompatible plasma is brought nullifies its toxic effect. While this statement is in agreement with the views of Lee,² it is interesting to find it contradicted in the recent report of the Interallied Surgical Conference,³ where it is stated that, "fatal accidents have occurred from agglutination of the blood corpuscles by the donor's plasma, but the danger of this is relatively small and it may be disregarded at an advanced post."

In spite of the apparent reliability of our best methods for matching donor and recipient, evidence steadily accumulates to the effect that these in vitro reactions are occasionally wrong. Thus Percy,⁴ using a slightly modified Kimpton-Brown⁵ tube, reports two transfusions with extensive hemolysis in a total of fifty-four cases, in which careful testing had shown no in vitro hemolysis. Neither of

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1. Moss, W. L.: J. A. M. A. **68**:1905, 1917. For more extended discussion and guide to literature see Moss, W. L.: Bull. Johns Hopkins Hosp. **22**:238, 1911.

2. Lee, R. I.: Brit. M. J. **2**:684, 1917.

3. Presse méd. **26**:193, 1918.

4. Percy, N. M.: Surg., Gynec. & Obst. **21**:360, 1915.

5. Kimpton, A. R.: Boston M. & S. J. **178**:351, 1918. Gives latest technic and refers to previous papers on the subject.

these cases had been transfused previously. McClure and Dunn⁶ report one death in 150 transfusions and ascribe it to "improper matching of the blood." Their technic for matching is reliable, and one infers another inexplicable reaction. These authors make a comment on gross hemolytic accidents which should be noted:

In the patients for whom many transfusions have had to be done, it has been observed that it is more and more difficult to find donors whose blood will match that of the patient. A donor may match perfectly early in the series of transfusions and later be found unsuitable. This is probably due to the development of isohemolysins. It is, therefore, most important that the blood be matched before each transfusion.

Our own experience will illustrate a case very much in point.

A. A., aged 13, with pernicious anemia and sepsis, required transfusion, Dec. 17, 1917. The mother desired to act as donor and was readily placed in Group 2. The patient's serum and cells behaved irregularly but he seemed to fall in Group 1. On matching directly against the mother a slight agglutination of the mother's corpuscles by the son's plasma was seen, the irregularity the son exhibited as a probable member of Group 1. This agglutination was so slight, so long in appearing, and the mother so insistent in her desire to act as donor that transfusion was done, her blood being taken into citrate, the plasma discarded and the red cells washed twice in accordance with technic described later in this paper. No chill followed this transfusion. There was rise in temperature of 1.8 degrees F., which was not appreciated by the patient.

Two days later the patient received a second transfusion of washed red cells from a Group 3 donor. These cells were entirely compatible. No chill, but a rise in temperature of 1.4 degrees followed this transfusion.

Next day an exactly similar transfusion from another Group 3 donor was given, without chill but with a rise in temperature of 2.4 degrees. Seven days later, and on the eleventh day following the original transfusion from the mother, a fourth transfusion of whole citrated blood was accomplished, using the mother as donor and omitting any effort to match the bloods. There was a severe and immediate chill, with a rise in temperature of 4.2 degrees, extensive hemoglobinuria and hemorrhage from the mucous membranes.

This reaction would have been avoided had there been an examination just prior to the last transfusion. It arose from the original use of slightly incompatible blood and a second employment of the same blood with a reasonable interval for the development of hemolysins. We have not seen a patient change groups under repeated transfusions and see no reason why he should, provided his original grouping and the grouping of his donors is as definite as the tests usually give. The rare cases, such as the one we have cited, where loose laboratory judgment first permitted injection of slightly incompatible blood and then did not insist on another test, should be excluded on the basis of the questionable first test. In such a situation at present we would use Group 4 donors, testing their cells against the patient's plasma and paying no attention to the exact final grouping of the patient.

6. McClure, R. D., and Dunn, G. R.: Bull. Johns Hopkins Hosp. 28:99, 1917.

Sydenstricker, Mason and Rivers⁷ report two cases tested by reliable methods in which exceptionally severe hemolysis occurred, death being ascribable to it in one case. In both instances several transfusions had been done previously. It is noteworthy that the fatal hemolysis followed a Lindeman⁸ syringe-cannula transfusion, and the nonfatal reaction a citrate transfusion. This has nothing to do with the merits of the two methods, but indicates that such reactions depend on inherent difficulties in the blood, which will be displayed no matter

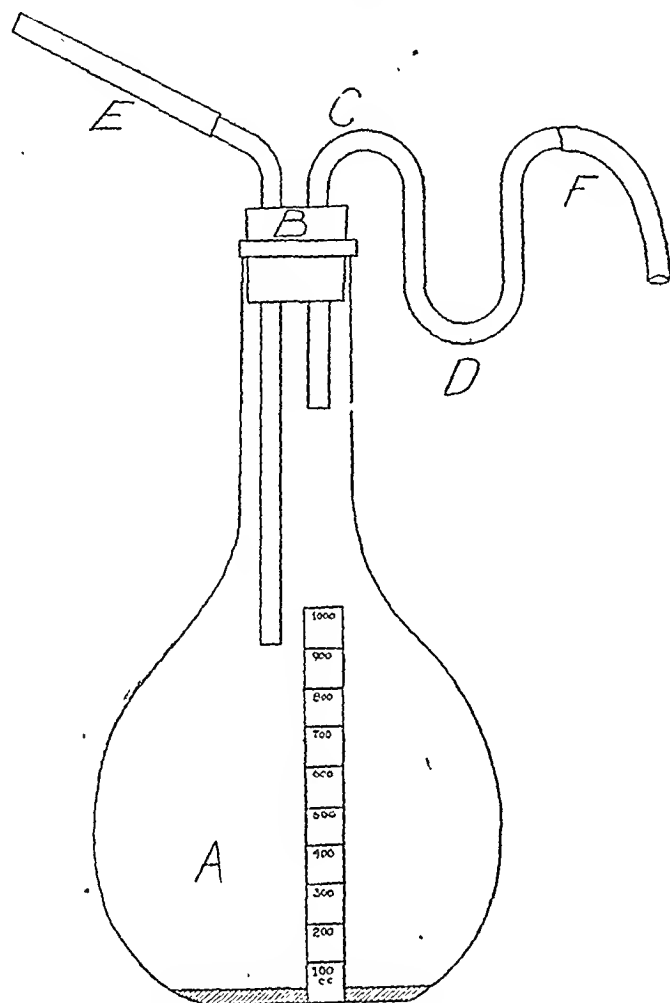


Fig. 1.—Collecting flask containing sodium citrate solution.

how the transfusion is carried out. It is thus apparently inevitable that with the best of testing, rare instances of extensive hemolysis will appear. These cannot be foreseen and have no relation to the method of actual transfusion. They form a foundation in all statistics of reactions, but they are not the type of difficulty with which we are most directly concerned.

The reactions following transfusion are of varied type. There may be slight headache, malaise, urticaria, slight fever, chills and high

7. Sydenstricker, V. P. W., Mason, V. R., and Rivers, T. M.: J. A. M. A. 68:1677, 1917.

8. Lindeman, E.: Am. J. Dis. Child., 6:28, 1913.

fever, appreciable hemolysis with hemoglobinuria, acute anaphylactic shock, etc. Out of this list of possibilities the most frequent noteworthy reaction is a rise in temperature, often accompanied by a chill. In our experience few patients undergo a rise in temperature of 2.5 degrees without subjective symptoms of some sort. A chill may precede such a rise, and it may fail to precede a rise of 3.5 degrees, but in this latter case other subjective symptoms will usually be present. In the cases which follow, a 2.5 degree rise of temperature has been the main criterion of a reaction, but since reaction possibilities are varied, this cannot be carried to mathematical finality. There is no single method of interpreting the harm done by injection of foreign protein, and in emphasizing the 2.5 degree rise criterion it is also necessary to mention other features of reactions when they become prominent.

No method of transfusion is reaction-free, and the reactions have been ascribed to a variety of causes, but without effort at experimental analysis. Lindeman⁹ is emphatic in his assertion that all febrile reactions following transfusions by his method are due to hemolysis. His substantiation of this statement depends on the fact that he has fewer reactions when hemolysis and agglutination tests of donors have his personal supervision. He presents no direct evidence that hemolysis has occurred in his unfavorable cases. Owing to the fact that reactions probably require very slight hemolysis, too slight to measure by our best methods, Lindeman's omission of direct proof is unavoidable. But it is not possible to hold that the only foreign protein in the blood stream after transfusion must be hemoglobin or, in a broader sense, hemoglobin and the stroma of broken down red cells. The early changes incident on blood coagulation result in the appearance of abnormal proteins, and there is no method of transfusion with the exception of vessel to vessel suture free from the possibility of their production. The conspicuous alteration which blood begins to undergo as soon as it leaves the vessels is clotting. Too frequently the setting of the clot is taken as the beginning and end of the act, but blood kept fluid, grossly apparently quite normal, may still have progressed some distance on the road to coagulation. There is no practicable method for citration of the large quantities of blood needed for transfusion which certainly prevents the early changes of coagulation. The methods in use simply arrest the process. The truth of this statement will be testified to by many who have used the citrate method with complete coagulation of the blood at a critical point in the transfusion. Similarly with the paraffined tubes of Kimpton and Brown,⁵ it is necessary to make the transfer before clotting spoils the operation, and here again there will be very few who have not occasionally lost

9. Lindeman, E.: J. A. M. A. 66:624, 1916.

a tube through the final act of coagulation. In like manner the syringe-cannula method⁸ even though carried through with the greatest neatness and dispatch must also present partial products of coagulation to the recipient. Abnormalities incident on coagulation vary widely from case to case, depending to some degree on the method and the skill with which it is carried out. They seem to be produced some time before the actual setting of the coagulum. That coagulation is a

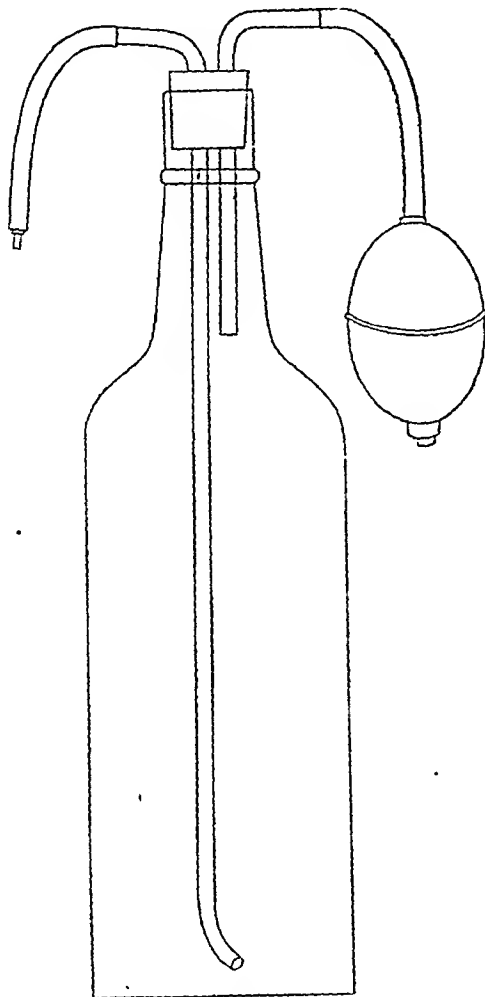


Fig. 2.—Injecting flask.

factor added to hemolysis in causation of reactions has been appreciated as a possibility by Satterlee and Hooker,¹⁰ by Minot and Lee¹¹ and by Robertson.¹² It is strongly indicated by the many comparative studies on plasma and serum reactions which are well summarized in recent papers by DeKruif¹³ and by Janeway, Richardson and Park.¹⁴

10. Satterlee, H. S., and Hooker, R. S.: *J. A. M. A.* **66**:618, 1916.

11. Minot, G. R., and Lee, R. I.: *Boston M. & S. J.* **177**:761, 1917.

12. Robertson, O. H.: *Brit. M. J.* **1**:477, 1918.

13. DeKruif, P. H.: *J. Infect. Dis.* **20**:717, 1917.

14. Janeway, T. C., Richardson, H. B., and Park, E. A.: *Archives Int. Med.* **21**:565, 1918.

Finally, if one makes a series of intravenous injections of a fairly constant type of foreign protein such as typhoid vaccine, he is impressed with the wide difference in reactions presented by different individuals. While in all a sufficient dose will give chills and fever, the severity of the reaction will vary widely. In the case of blood transfusion, the foreign proteins presented are infinitely less toxic than the typhoid bacillus, and there is a consequently wider range of reaction possibilities, a range which could only be presented by high dilutions of typhoid vaccine. Thus, there will be many individuals who are entirely unaffected, there will be others giving minor and negligible reactions, and there will be a final group who react in accordance with our criterion by a temperature of 2.5 degrees or over. The capacity for foreign protein production probably varies in different coagulating bloods, though at present we have no method of directly estimating it. We feel that this possibility is of less importance than the condition of the recipient and would be much interested to see this phase of the question attacked experimentally.

Before approaching our experimental data, it is worth while to sum up the most recent reaction statistics. Lewisohn¹⁵ reports a "chill following the transfusion" in 10 per cent. of seventy-five instances. Meleney, Stearns, Fortune and Ferry¹⁶ regard the typical reaction as a "chill coming on about one-half hour after the transfusion, a sharp rise in temperature, gradually subsiding to normal in three to eight hours . . ." Their transfusions meriting statistical consideration are as follows:

Citrate Method	No. of Reactions	Per Cent. of Reactions
196	127	64.8
Syringe-Cannula		
73	47	64.4

The reactions are not figured on a 2.5 degree rise in temperature, but comprise all noticeable disturbances in patients under uniform hospital observation following the transfusion. They are significant in the parallelism between citrate and syringe-cannula administration.

Sydenstricker⁷ et al. report 100 citrate transfusions with only 17 per cent. of reactions of any sort, from the mildest malaise to the most extreme "chill, stupor and hemoglobinuria." Their observations are on hospital patients under uniform conditions and the figures the lowest given for the citrate method. Lewisohn's¹⁵ 10 per cent. of chills will certainly mean at least another 10 per cent. of distinctly noticeable reactions.

15. Lewisohn, R.: *Ann. Surg.* 64:618, 1916.

16. Meleney, H. E., Stearns, W. W., Fortune, S. T., and Ferry, R. M.: *Am. J. M. Sc.* 154:733, 1917.

Lindeman⁹ reports 155 syringe-cannula transfusions with a rise in temperature of two or more degrees in 30 of them, or 19 per cent. Minot and Lee¹¹ in 92 transfusions "most of them given by the Vincent paraffin tube method," a modification of the technic of Kimpton and Brown,⁵ report 37 reactions of varied severity, or 40 per cent. These reactions cannot be analyzed in terms of a definite rise in temperature. Unfortunately, there are no exact observations as to reactions in large

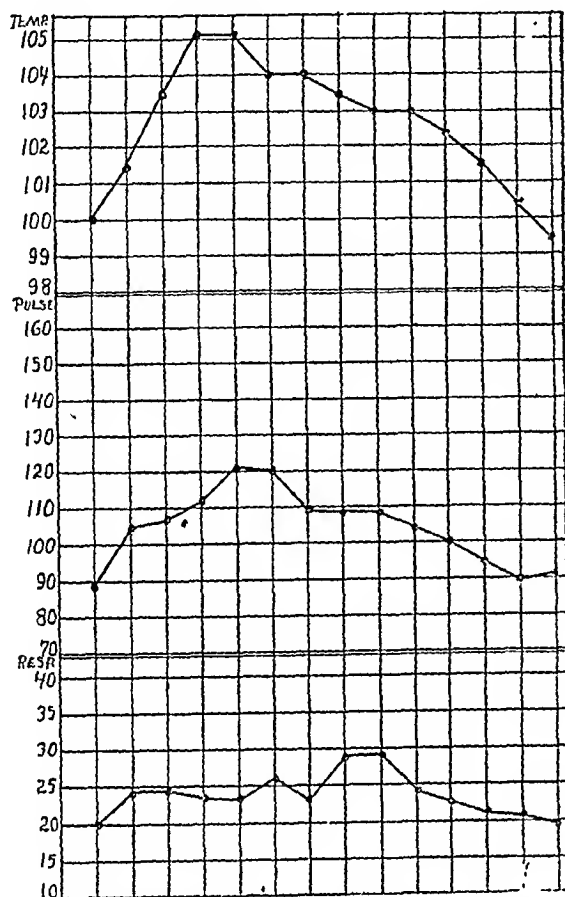


Fig. 3.—M. C.: Pernicious anemia. Group 3. Donor L. F., Group 3. Injection of entire cell content of 600 c.c. donor's blood at start of curve. Abscissae represent half hour intervals; ordinates, temperature, pulse and respiration.

numbers of cases transfused by this method. At the Brigham Hospital, in 19 cases so transfused we have had a temperature rise of 2.5 degrees in 21 per cent.

Our experience with transfusion by the citrate method gives a larger number of reactions than are reported elsewhere. Out of 83 transfusions we have had a rise in temperature of 2.5 degrees 50 times, or 60 per cent., and of this number 39, or 47 per cent., have had chills. These figures include all the transfusions of whole citrated blood which have been done by different individuals at the Brigham Hospital. In order to test the matter further we have done 17 such

transfusions, using the most extreme care in our effort to reduce the reaction percentage. In these transfusions there were 9 rises in temperature above 2.5 degrees, or 53.3 per cent., and 7 chills, or 40 per cent.

It is impossible to summarize these very discordant reports. In totality it would seem that both the syringe-cannula and paraffined tube methods offer fewer reactions than the citrate method. We should count ourselves fortunate could we reduce reactions from transfusion of whole citrated blood to 45 per cent., but it is proper to note that there would be no missed reactions in this group since we have demanded very rigorous post-transfusion observation. We have seen temperatures rise 3 degrees and become normal in three hours, and such reactions will escape notice if frequent observation is not the rule.

TECHNIC

1. *Methods of Recording.*—It is our custom to take temperature, pulse and respiration at the time of transfusion and at half-hour intervals afterwards until the temperature has returned to its original level or given positive indication of soon reaching it. We have seen a number of 2.5 degree rises in temperature accompanied by inconspicuous malaise which would have been missed by ordinary morning and evening temperature taking. For routine work such close following is unnecessary, but for analyzing reactions it is imperative and will, we are sure, disclose many unsuspected increases in temperature.

2. *Methods of Transfusing and Handling Blood.*—A. The Citrate. Four different specimens of sodium citrate have been used, one of unknown origin and probably "commercial" in grade, two from well known firms certified as C.P., and a fourth made especially for us in the Boylston Chemical Laboratory of Harvard University, recrystallized a number of times and probably as pure a product as can be obtained. The number of reactions resulting from all these specimens is the same. There is no peculiarity inherent in certain specimens of sodium citrate which can cause trouble.

B. Citration. A variety of methods has been used and in our hands none of them reduces the number of reactions. The cleanest and best seems as follows. A one liter Florence flask, A (Fig. 1), containing 35 c.c. of 8 per cent. sodium citrate is stoppered with gauze and autoclaved for fifteen minutes at 15 pounds. This does not alter the reaction of the citrate or its ability to prevent coagulation. A rubber stopper, B, carrying two glass tubes is boiled together with a No. 19 needle and the rubber tubes, E and F. E delivers blood to the flask and should not be more than 5 inches long since it is desirable to eliminate as much contact of blood and rubber as is possible. F allows the operator to exert suction. This apparatus avoids stirring the blood and contact with the air. It delivers the blood through the long glass tube directly into the citrate without dripping slowly down the sides of the flask, and the suction facilitates collection very markedly. Thirty-five c.c. of 8 per cent. sodium citrate should keep fluid 1,400 c.c. of blood. It gives the patient 2.8 gm. of citrate, a dose far below the dangerous limit. Such citration insures a strength great enough to restrain coagulation in the 800 or 900 c.c. of blood ordinarily withdrawn, and after repeated observations we are assured it causes no hemolysis within three hours' time. Citration has also been accomplished by using 2.5 per cent. sodium citrate in freshly distilled water in the proportion of 10 c.c. to 90 c.c. of blood, and a 2 per cent. solution in the same proportion. These alterations do not

change the frequency of reaction occurrence. Transfusions have varied in amount from 250 to 950 c.c. We have observed no definite connection between amount of transfusion and extent or frequency of reactions.

C. Injection. The apparatus in Figure 2 is used. It is convenient to clean and carry about and brings the blood in contact with a minimum amount of rubber. A fine needle, No. 21, is thrust into the recipient's vein and with blood flowing freely connection can be made and the donor's blood driven in. Robertson¹² has recently pictured a combination removal and injection apparatus very convenient for emergency work. As routine, however, we believe the blood should be filtered before the final injection. This is readily accomplished by filtration from our collecting flask into the injecting flask, an old,

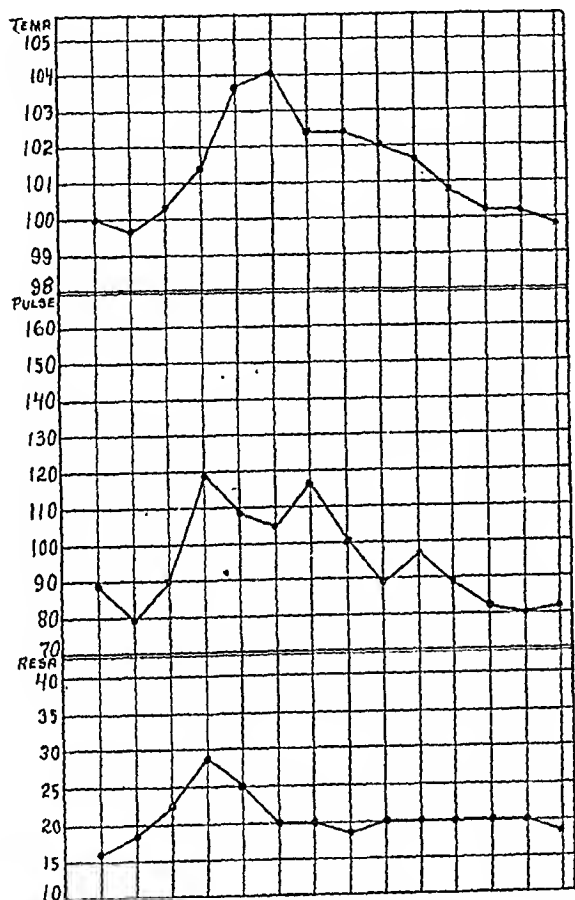


Fig. 4.—M. S.: Chronic nephritis and hypertension. Injection of entire cell content of 700 c.c. own blood at start of curves. Abscissae represent half hour intervals; ordinates, temperature, pulse and respiration.

fine mesh, sterile towel being used. All glassware, both for collection and injection, is cleaned in hot tap water and rinsed with fresh glass distilled water before being tied up for sterilization. Needles and short delivery tubes have been boiled in tap water and shaken dry before use. For all solutions coming in contact with blood, glass distilled water has been used, but flasks containing sterile citrate have frequently stood some days before using. As will be seen later, all salt solution used for direct injection has been made from water distilled and sterilized on the day of use. While it is probable that chills would be induced by 100 c.c. injections of old citrate, our quantities have been 25 or 35 c.c., except in a moderate number of instances when precaution has been taken to have fresh material.

EXPERIMENTAL

1. Does the cause of the reaction reside in cells or in plasma?

At the outset we felt confident that the plasma would be found at fault, but this is far from being the case. Citrated plasma, thoroughly freed from all formed elements by prolonged high speed centrifugalization or by porcelain filtration is singularly nontoxic, contrasting markedly with serum in this regard.

The following transfusion repeated four times on three different patients with pernicious anemia, two of whom were subsequently transfused without reactions by other methods, illustrates the beginning of the answer to Question 1.

Patient M. C., Group 3. Donor L. F., Group 3. Donor bled 600 c.c. into 35 c.c. of 8 per cent. sodium citrate at 11:15 a. m. Blood at once centrifugalized at high speed, the plasma pipetted off and the *entire* cell content washed twice with *freshly made* and freshly sterilized physiologic sodium chlorid solution (0.85 per cent. NaCl). This washing was accomplished in 250 c.c. milk bottles in a large high speed centrifuge, with every precaution as to sterility. The plasma was discarded and the cells brought up to 300 c.c. volume with salt solution and injected into the patient at 1:23 p. m. A characteristic and severe reaction followed. (Fig. 3.)

This experience was repeated on L. T. and T. M., who had never been transfused previously, save that four washings were used instead of two, and in all cases the reactions were identical. Not that there was no attempt to separate the different formed elements of the blood. The injection contained washed red cells, white cells, plates and salt solution, and some one or several of these elements caused the reaction.

In which of the cellular elements does the reaction reside? Defibrination completely eliminates blood plates and markedly reduces the white count. We have done transfusions with washed red cells from defibrinated blood and have markedly reduced our reactions. A full discussion of these transfusions appears later and is mentioned here simply to indicate that salt solution, red cells, white cells in greatly reduced numbers (a reduction to about one-third is our ordinary experience in defibrination) and no plates make the most perfect blood for transfusion we have used. It is sufficient to wash these cells twice. We have not been able to get any satisfactory plate-free, leukocyte-rich preparations for use. Whether one makes the separation by means of defibrination or by means of differential centrifugalization, the plates and white cells are eliminated together, but we have seen enough fairly high white counts in our defibrinated washed cell transfusions to be ready to consider the white cells very slightly at fault, if at all.

Thirty transfusions have been done taking the blood into citrate, centrifugalizing slowly for five minutes, removing the plasma and washing twice. At the termination of the last two centrifugalizations

carried on at highest speed, all "buffy" material was removed from the red cells. Such technic reduces the white cell count below half and plates are found with the greatest difficulty. It is impossible to consider such preparations plate-free, but the number of plates left is certainly exceedingly small. In this series, eleven, or 40 per cent., have had the 2.5 degree rise in temperature and six, or 20 per cent., have had chills. We have reduced the number of reactions as compared with whole citrated blood but are still far from eliminating the difficulty; indeed, our percentage is noticeably worse than many observers have reported with whole blood. As far as is known, blood plates exist to aid in blood coagulation, and to perform this function it is necessary for them to begin to change as soon as blood is shed. Wright and Minot¹⁷ have recently called attention to a definite type of platelet metamorphosis. Citration seems to prevent this type of change quite effectually. We have repeatedly examined plates in citrated plasma and are impressed with the extraordinarily small amount of agglutination which takes place. In no way can one obtain more beautiful plate preparations than by staining smears of such plasma with Wright's stain. Since the plates are the principal formed elements eliminated in this type of transfusion, it is natural to look to them for some share in reaction causation but the absence of any particular morphologic change, coupled with the following experiences, indicate that these elements are only partially to blame. We have made ten injections of platelet suspensions with three, or 30 per cent., of 2.5 degree reactions and two chills. These suspensions have been made in a variety of ways and no method of handling which could in any way imitate the condition of the plates in whole citrated blood has resulted in a uniformly toxic product. The conclusion is thus forced that these formed elements are contributors to the total number of reactions but by no means the sole cause. The type of agglutinative metamorphosis pictured by Wright and Minot¹⁷ does not necessitate toxicity. Injections with this change present have been innocuous and injections containing the plates as isolated structures, morphologically normal, have caused reactions. Two cases of true hemophilia have been treated by combined plasma and plate injections without reaction and with prompt cessation of bleeding. In these instances the washed red corpuscles have been introduced next day. In ten transfusions the citrated plasma has been removed, cleaned of formed elements by one hour to one and one half hours of high speed centrifugalization, the red cells washed twice with thorough removal of "buffy" coat, the cleaned plasma and washed red cells mixed and injected. There have been four, or 40 per cent., of 2.5

17. Wright, J. H., and Minot, G. R.: *J. Exper. Med.* 26:395. 1917.

degree reactions and two chills. The addition of cleaned plasma to washed corpuscles and salt solution gives a reaction percentage identical with that obtained from washed corpuscles and salt solution alone.

2. Is the reaction due to some unsuspected factor against which we do not test our donors?

In an effort to answer this question the following transfusions have been done.

M. S. Chronic nephritis and hypertension. Bled 700 c.c. into 25 c.c. 8 per cent. sodium citrate. Plasma discarded. Entire cellular content washed four times, brought to 700 c.c. volume with physiologic saline solution and reinjected. A characteristic reaction followed (Fig. 4).

This result was repeated on J. M., chronic arthritis, and these two cases of plasmapheresis¹⁸ in which the *entire cellular content* had been washed and returned to the same individual are identical with the transfusions containing washed whole cell content mentioned earlier in this article.

It is significant that out of six instances of washed whole cell content injection we have had six chills and pronounced febrile reactions, all well above 2.5 degrees. In two cases of chronic arthritis under treatment with intravenous typhoid vaccine we have withdrawn 550 c.c. of blood into 25 c.c. of 8 per cent. sodium citrate, have filtered this blood into an injecting flask and returned it to the same individual. In one instance there was no reaction whatsoever; in the other there was a rise in temperature of 1.2 degrees, but nothing appreciable to the patient.

Finally, with Dr. J. P. O'Hare, we have done plasmapheresis in chronic nephritis eighteen times, taking the blood in citrate, washing twice and returning the red cells freed as far as possible from plates and leukocytes. The technic corresponds exactly with that used in the transfusions of washed red cells from citrated blood. A detailed account of this work appears in another article. Here it is of interest because not one of these patients had a chill or a rise in temperature of 2.5 degrees. The majority reacted slightly, and in four cases there was a rise above 2 degrees. All were cases of advanced chronic nephritis, and while such individuals may be less reactive than the anemic cases making up the bulk of our figures, the results would seem to indicate that handling of perfectly compatible red cells with minimal exposure to citrate does not induce alterations of marked grade. A further consideration of these cases appears in the final discussion.

3. Does citration alter the erythrocytes so as to render them more susceptible to hemolysis when injected?

18. Abel, J. J., Rowntree, L. G., and Turner, B. B.: J. Pharmacol. & Exper. Therap. 5:625, 1914.

Two sets of transfusions bear on this point. In fifteen instances we have taken the blood from donors into our ordinary collecting flasks and have defibrinated at once by shaking with glass beads. This removes all the plates and reduces the white cell count to about one-third. The red cells have been centrifugalized off, washed twice, brought up to original volume with physiologic sodium chlorid solution and injected. These transfusions have given three, or 20 per cent., reactions of 2.5 degrees with one chill, decidedly better figures than we can obtain by any citrated transfusion. They may be contrasted with nine transfusions in which all procedures have been identical except that 25 or 35 c.c. of 8 per cent. sodium citrate have been added to the final red cell suspension one or two hours before injection. In these cases we have had four, or 44 per cent., reactions above 2.5 degrees, with two chills. It would thus seem that the mere addition of a normal dose of citrate to red cells develops slight abnormality. We have been unable to detect the nature of this change. Many histologic examinations of citrated blood and of washed citrated red cells have failed to disclose any abnormalities. As far as whole citrated blood is concerned, this has been the experience of others.¹⁵ When the fragility of red cells, taken from defibrinated blood to which citrate has been added in concentration comparable to that used in transfusion, is compared with cells from the same blood which have not been subjected to citrate, it is frequently but not always found that the citrated cells hemolyze more readily. In our experience the reaction has never gone the other way, provided the conditions of citration are kept comparable to those used in transfusion. The two sets of tubes are identical or the citrated cells, as is more frequent, show greater hemolysis. But this observation does not enable us to predict when reactions will occur. We have seen a pronounced increase in fragility of our red cells exposed to citrate and no reaction whatsoever on the part of the recipient. The increase in fragility simply indicates that exposure to sodium citrate tends to produce abnormal red cells. Clowes¹⁹ has called attention to the similarity of sodium chlorid and sodium citrate in their general effects on protoplasm. The difference between the salts is a function of the anion and the citrate is infinitely more toxic than the chlorid no matter what the test material. It is of further significance that ionized salts of calcium such as calcium chlorid readily neutralize or counteract the effects of both sodium chlorid and sodium citrate. If these facts are applied to the question of transfusion of citrated blood the following considerations are developed. In collecting the blood into sodium citrate care is taken to have a sufficient excess to abolish thoroughly all possibility of

19. Clowes, G. H.: *J. Physical Chem.* 20:407, 1916.

calcium effect in bringing about coagulation. It is of prime importance that calcium be eliminated entirely, and in some way, not thoroughly known, the addition of sodium citrate does thoroughly remove ionized calcium. Conditions are at once favorable for the action of the sodium citrate and, indeed, of the sodium chlorid on the red blood corpuscles. What the nature of this action may be we cannot say. The increase in fragility which we have mentioned indicates that some change occurs. Robertson¹² has used 160 c.c. of 3.8 per cent. sodium citrate in his recent work in France. The figure is chosen because it gives with the 500 or 800 c.c. of blood usually taken an osmotic pressure approximating that of 0.85 sodium chlorid and isotonic for the red corpuscles. While this may be a wise precaution, it does not meet the true biologic difficulty with the citrate. Citrated blood such as we have used does not contain corpuscles damaged by abnormal osmotic relations, but corpuscles damaged by sodium citrate operating as a specifically harmful substance. Unfortunately, no studies exist giving data exactly analogous to those for which we have suggested a necessity. There are many comparisons between the hemolytic effects of various salts in equimolecular solutions. Thus, recently, Chauffard and Huber²⁰ have compared the hemolytic effect of Ringer's solution, sodium chlorid, magnesium chlorid, etc., taking care to have an identical freezing point throughout their entire series of comparisons. They have again demonstrated that these salts do not act by virtue of alterations in osmotic pressure, but through individual differences, the final nature of which are unknown. What is called for in the solution of such a question as arises here, is comparison of the fragility of red corpuscles by means of one type of solution, such as varying concentrations of sodium chlorid, after immersion under constant conditions in a variety of equimolecular solutions of sodium citrate, sodium acetate, sodium oxalate, etc.

It is clear at once that, provided sodium citrate produces abnormality in red cells, rendering them more susceptible to hemolysis, we cannot be surprised at the failure of sodium chlorid, a substance acting in the same way, but to a less degree, to wash out the effect of citrate. Thus, in our thirty transfusions of corpuscles taken into citrate and washed in physiologic sodium chlorid solution we have had 40 per cent. of reactions. If after the second washing calcium chlorid is added to the salt solution, making a concentration of 0.025 per cent. calcium chlorid analogous to Ringer's solution, and in this a third washing and the final suspension of the corpuscles for injection is carried out, there is still no reduction in the number of reactions in transfusions. It would seem, therefore, that the change

20. Chauffard, A., and Huber, J.: *Presse méd.* 26:141, 1918.

induced by citrate in the protoplasmic system represented by the red corpuscles is irreversible by calcium within the time of exposure used — from one to three hours.

DISCUSSION

Our interest in this question arose from a desire to get information on the best type of blood modified for injection which could be prepared. If it were true that the plasma from blood which has passed through the manipulations necessary for collection contained all or most of the toxic products involved, the problem would be simple. A nontoxic blood, always excepting detectable disasters from agglutination and hemolysis, could be obtained by simple washing of compatible red cells. Unfortunately the reverse is true, plasma being nontoxic and cellular elements varying in toxicity. We believe that one element in the appearance of this toxicity resides in the plates, which begin to become abnormal as soon as they leave the vessel. The grade of abnormality of these elements depends to some degree on the extent and skill of the handling which they are compelled to undergo in varied methods of transfusion. On this phase of reaction causation will depend the fact noted by others that dexterity in any type of transfusion means fewer reactions. The change which the plates undergo is not evidenced by any characteristic morphology, nor is it possible to get a high percentage of reactions from plates alone. But here one is faced by two difficulties. The first is the impossibility of getting all of the plates out of a blood collected for transfusion and manipulating them so that injection is safe. Their extraordinary agglutinative power makes it very difficult to obtain fair sized injections of washed plates which are free from large masses. Second, the thromboplastic material which the plates present makes a proper degree of hesitation necessary, since intravascular coagulation is too dangerous an outcome to be viewed lightly. The platelet injections which we quote are the result of a gradual increase in dose and the reactions obtained have required the maximum yield of from 500 to 650 c.c. of citrated blood. Such injections always contain many leukocytes, but our experiences have never pointed to these elements as important factors in the development of toxicity. Finally, in regard to the plates and leukocytes, it should be noted that we have no tests for agglutination or lysis of these elements, and the possibility that unexpected incompatibilities may reside in them should be borne in mind.

If we consider that our efforts to remove plates from citrated blood by differential centrifugalization have been successful, and histologically they are so, it is evident that red cells exposed to citrate in collection are more apt to cause reactions than those taken from

defibrinated blood and subjected to a comparable amount of washing, 40 per cent. of reactions occurring in the first case and 20 per cent. in the second. If to these last cells citrate is added as the single difference in their treatment, the reactions again become 44 per cent. Citration, therefore, seems to harm red cells and possible direct evidence for this exists in the occasional promotion of fragility by the substance. The indication is that hemolysis contributes a certain number of reactions but that this hemolysis is too slight to be detected by direct methods.

The results with plasmapheresis confirm our transfusion experiences insofar as injection of washed whole cell blood is concerned. There is, however, a wide discrepancy between plasmapheresis using citrated blood with platelet elimination, and transfusion embodying similar maneuvers. In these latter there is no possibility of cellular incompatibility so slight as to be unrecognized. If citration results in greater cellular fragility, it will do its minimum of harm in these injections, whereas in transfers between different individuals it is possible that an influence which promotes fragility even very slightly may result in a degree of hemolysis of sufficient magnitude to cause reaction. We have suggested that the cases of chronic nephritis which have been subjected to plasmapheresis may be less reactive than are the anemias. Without transfusion of a series of these cases no definite statement can be made. Certainly in our hands cases of secondary anemia from simple bleeding or from bleeding plus carcinoma have reacted as freely as have the primary anemias. The final factor of the individual in these reactions is as yet almost unknown. The tests for agglutination and hemolysis present a certain amount of valuable qualitative information in this direction, but beyond these we cannot go.

SUMMARY

1. Reaction figures are given for various methods of transfusion. Those for the citrate method are widely divergent, but in the main exceed the results obtained by paraffin tube or syringe-cannula methods.

2. A rise in temperature of 2.5 degrees F. is suggested as the best criterion of a reaction, and the technic used in citrate transfusions is discussed.

3. The number of reactions bears no constant relation to method of citration or specimen of citrates.

4. Citrated plasma free from formed elements is nontoxic in compatible individuals.

5. Washed whole cell content of blood is uniformly toxic, whether injected into the individual from which the cells have been removed

(plasmapheresis) or into different individuals who have been tested and show no agglutination or hemolysis of red cells.

6. Removal of the plates and two-thirds of the leukocytes from citrated blood by differential centrifugalization with final suspension of the red cells in freshly made sterile physiologic sodium chlorid solution has resulted in 40 per cent. of reactions in thirty transfusions.

7. Removal of the plates and a comparable number of white cells by defibrination, with thorough washing and suspension of the red cells in similar saline solution has resulted in 20 per cent. of reactions in fifteen transfusions.

8. Addition of citrate from one to two hours before injection to transfusing blood so prepared has resulted in 44 per cent. of reactions in nine transfusions.

9. While the totals of the different types of transfusions which have been employed are not large, it appears that three elements make up the final total of reactions in citrate transfusion: (a) very rare gross incompatibilities which escape in vitro detection; (b) changes in the plates, part of the process of coagulation; (c) direct action of the sodium citrate on red cells promoting hemolysis.

THE CHRONIC FORM OF MENINGOCOCCUS MENINGITIS *

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Cerebrospinal meningitis with a prolonged course presents two varieties. In one we observe only recurrences or episodic meningeal manifestations. Here the patient during the intervals appears to be in perfect health. Nevertheless, suddenly or insidiously the symptoms return either in a slight or grave form. The intervals may last either a few days or a few weeks.

The other variety which is the subject of the present contribution, concerns cases of cerebrospinal meningitis the evolution of which is continuous. While in the literature are mentioned a few such isolated cases under different captions, nevertheless their chief characteristic features have not been sufficiently emphasized by various authors with the exception of Robert Debré, pupil of Netter. In 1845 Tungal¹ for the first time speaks of disturbances in the brain tissue proper in the course of a prolonged case of cerebrospinal meningitis. The next two earliest records we find by Rilliet² and Merkel.³ They both speak of chronic hydrocephalus following a very prolonged course of cerebrospinal meningitis. Since then a number of records have accumulated in the German, French and American literatures indicating various isolated complications in the central nervous system. The present contribution is based on a study of ten cases of meningitis of the meningococcus type kept under observation for several years. Eight of these cases came to necropsy, so that in the largest majority of the series, clinical as well as anatomic data were available for consideration. The cases are very briefly as follows:

REPORT OF CASES

CASE 1.—M. S., man of 27, mason, had a typical attack of epidemic cerebrospinal meningitis. The meningococcus was found. The spinal fluid presented polynucleosis and increase of albumin. The acute stage lasted eight days. There was a remission, but some rigidity of the neck remained. There was an exacerbation during five days, with remission again and a gradual deterioration, and muscular atrophy with a paretic condition, ataxia of all extremities,

* Read at the meeting of the American Neurological Association, Atlantic City, N. J., May 9-10, 1918.

1. Tungal: Cited by Ebstein, *Deutsch. Arch. f. klin. Med.*, 1908, **93**, 241.
2. *Arch. Gén. de Méd.*, 1847.
3. Merkel: *Deutsch. Arch. f. klin. Med.*, 1866, **1**.

knee jerk diminished, decubitus, pain in the legs, mental dulness, deafness; spinal fluid almost clear, with mononucleosis. The patient lived five months. Necropsy report is given later.

CASE 2.—O. O'B., man 31, a laborer, had the usual acute onset. He had nine exacerbations during six months. In the intervals he developed amyotrophy with contracture of the limbs in flexion. There was decubitus in the occipital region, incontinence of sphincters; no spinal fluid was obtainable. There was deafness, palsy of internal recti in both eyes, mental hebetude, an occasional delirious state. The patient died in convulsions. No necropsy.

CASE 3.—M. S., girl, aged 25. Typical form. The patient had five exacerbations during ten months. There was amyotrophy with paresis of the lower extremities, contracture in flexion, incontinence; reflexes (tendon) diminished; deafness; impaired vision; palsy of left external rectus. Very little spinal fluid was obtainable, which was very slightly turbid. There was mononucleosis. The meningococcus was not found. The patient assumed a stuporous state. Necropsy.

CASE 4.—B. G., man aged 25, a watchmaker. Typical form. He had three exacerbations in four months; amyotrophy; paresis of all limbs; tendon reflexes much diminished; decubitus; pain in the lower extremities; deafness; vision impaired; incontinence; mental hebetude. Very little spinal fluid was obtainable on lumbar puncture and no meningococci were found. No necropsy.

CASE 5.—S. D., a man aged 29 years. Typical form. He had six exacerbations in thirteen months. The condition following each successive exacerbation was worse than the preceding. All the characteristic symptoms were pronounced, namely, amyotrophy, decubitus, contracture in flexion; knee jerks plus; deafness; palsy of left external rectus. No spinal fluid could be obtained after several attempts. Mental dulness. Necropsy.

CASE 6.—A. G., a boy, aged 19. Typical form. He had three exacerbations in six months: amyotrophy with flexion contracture of the legs was so pronounced that the knees touched the chin. The knee jerks were lost. There was incontinence of urine and feces and decubitus; spinal fluid very slightly turbid; mononucleosis; meningococcus not found; mental hebetude. Necropsy.

CASE 7.—C. S., a man, aged 32. Typical form. Had five exacerbations in ten months. Amyotrophy with contractures of lower limbs; decubitus; mental dulness, with periods of improvement; incontinence; spinal fluid clear, no meningococci, but mononucleosis; palsy of internal recti in both eyes; mental dulness. Necropsy.

CASE 8.—A. P., girl, aged 22. Typical attack. She had three exacerbations in five months. Amyotrophy with mild contracture of legs and paretic condition; knee jerks diminished; incontinence; deafness; impairment of vision; mental hebetude, but at times total lucidity; delirium with each exacerbation and a mild confusional state at times in the intervals; spinal fluid clear; mononucleosis. Died suddenly. Necropsy.

CASE 9.—J. O'H., boy, aged 13. Typical form. He had five exacerbations in two and a half months. Amyotrophy with contracture of legs; incontinence; decubitus; impairment of vision; spinal fluid clear, but with a yellowish tint; mononucleosis; mental dulness, with occasional mild delirium. Necropsy.

CASE 10.—S. H., girl, aged 7. Typical form. Six exacerbations in four months; amyotrophy with contracture of legs in extension; extreme emaciation; incontinence; mental dulness with occasional complete lucidity; spinal fluid clear, with a yellowish tint; mononucleosis; impairment of vision; palsy of the right external rectus; died in convulsions. Necropsy.

A detailed analysis of these cases brings out the following important anatomic and clinical facts.

Pathology.—The anatomic-pathologic findings in the eight cases that came to necropsy are as follows: The condition of the meninges could be characterized as one of diffuse pachymeningitis: irregularly distributed patches of thickened membranes could be seen, especially along the larger blood vessels and mostly at the base of the brain and near the cerebellum. The blood vessels appeared congested. Purulent areas were not frequent but if they occurred, were seen particularly at the level of the chiasma. Adhesions between the dura and the pia-arachnoid, as well as between the latter and the cortex, were occasionally seen, but more frequently the pia could be detached from the cortex without tearing the tissue of the latter. In several of the cases small cystic collections were found at the level of the pons.

The brain itself appeared on palpation somewhat softer than normal. It was due to dilatation of the lateral ventricles. In all the eight cases they were filled with considerable quantities of turbid fluid, and in two of these cases it was frankly purulent. There was apparently little or no communication between the various ventricles, as they were all overfilled with fluid. The histologic examination revealed in the meninges the usual findings of a chronic inflammatory state, namely, large masses of fibrous tissue with leukocytic infiltration of the walls of the blood vessels. In the cortex besides an edematous condition there was also infiltration of the blood vessels and proliferation of neuroglia. A certain degree of chromatolysis was evident throughout.

In the spinal cord, thickening of the meninges with meningeal adhesions in isolated areas were seen over the posterior aspect of the cord and especially at the level of the cervical and lumbar segments. The spinal fluid was less turbid than that of cerebral ventricles and sometimes very clear. The tissue of the cord suffered only at the periphery close to the altered meninges. Leukocytic infiltration with dilatation of some blood vessels was observed. Of special interest are the alterations found in the roots, more in the posterior than in the anterior ones, and in the nerve trunks. Leukocytic infiltration of the latter's blood vessels and actual degenerative changes in the nerve fibers were in evidence. Specimens were taken at the level of the cervical and lumbosacral segments. Portions of individual nerves of the brachial and sacral plexuses were examined. Chromatolysis was present in the posterior spinal ganglia.

The cerebrospinal fluid deserves special mention. I have already spoken of the appearance of this fluid and of its greater turbidity in the ventricles than in the subdural space of the spinal cord. In the latter I found it to be somewhat yellowish in two cases, but in the majority of the cases it was clear. Other writers observed the change of turbid to clear fluid in prolonged cases, although it is not so in every

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case. Hajek,⁴ for example, observed during an epidemic of cerebro-spinal meningitis in Milan clear fluid at first, then later purulent and then again clear. Netter and Debré⁵ in their extensive studies also report such occurrences in rare cases. Albumin was found in the earlier stages of the disease in large quantities; in the later periods, three and four months after the onset, the albumin content was negligible. The polymorphonuclear cells of the early periods disappeared and mononucleosis was almost exclusively found weeks later. The same condition was found with regard to the meningococci. While they were abundant in the beginning, their number gradually became smaller and smaller, and several weeks later they were very rare. Cultures made in three cases from the spinal fluid, respectively six, eight and nine weeks later, failed to reveal the presence of the micro-organism. The disappearance of the meningococcus ran parallel with the clearing up of the spinal fluid. Other authors, however, reported the occasional presence of the micro-organism in perfectly clear fluids. Hajek⁴ made daily punctures in a child of 3 during eight days; the spinal fluid was invariably clear and still a few meningococci were found, but curiously enough they were extracellular instead of being included in the cells.

Clinical.—The clinical picture based on the ten cases presents the following chief characteristics: The onset shows nothing unusual worth mentioning. The initial symptoms gradually subside and to all appearances recovery is expected, but close observation reveals that it is only a remission, as there are still physical and mental manifestations sufficiently evident to consider the patient ill; some rigidity of the neck and of spine, some difficulty of walking are all present. Mentally the patient shows a diminution of attentive power, of the mnemonic faculty and of general intelligence. The remission may last various times. In my cases from nine to twenty-one days. In the midst of the apparent amelioration of the symptoms there is suddenly or rapidly a reappearance of the manifestations characteristic of the acute stage: the foregoing mental and physical symptoms become accentuated and fever is added. Again, this symptom group will gradually subside for a period of one or several weeks, but nevertheless will not totally disappear. The curve of accentuation and amelioration of the condition may repeat itself an indefinite number of times. Gradually one observes the development of special disturbances which are so constant that they may be considered as characteristic of the

4. Hajek: *Pediatrics*, January, 1909.

5. Netter and Debré: *Bull. Soc. méd. d. hôp.*, Paris, July 29, 1899, and May 11, 1900.

chronic form of meningococcus meningitis. They are seen in the motor, sensory, trophic and psychic spheres.

The most conspicuous change takes place in the state of *general nutrition* and especially in that of the musculature of the body. It is diffuse and not confined to any one area. The limbs become extremely thin, the usual roundness about the shoulders and hips disappears and the bony processes are very conspicuous. The subcutaneous fat disappears and the bones appear to be covered with a thin and wrinkled segmental covering which is dry and without the usual elasticity. Erythematous and herpetic disorders readily develop. Decubitus in the sacral, in the occipital (one case) regions and also on the heels are common.

Motor disturbances are especially evident in a body affected with a marked amyotrophy. The neck becomes more rigid than formerly. The limbs are in a state of contracture and in flexion and thus the patient remains immobile. In Case 6 the contracture and rigidity were so pronounced that the patient was all doubled up, with his knees almost reaching the chin. In less contracted limbs (Cases 2, 3, 5, 9 and 10) movements are possible, but there is a distinct paretic condition with diminished reflexes, and the movements remind one of those which are observed in cerebellar affections, namely, ataxia or awkwardness. In only one case (5) the knee jerks were increased, but there was no ankle-clonus and no toe phenomenon. In all the other cases the knee jerks were diminished, and in Case 6, with extreme contracture, the patellar tendon reflex was not obtainable.

Sensory disturbances are observed chiefly in the subjective field. Rigidity, with pain in the neck, spontaneous paroxysms of pain, especially in the cervical and dorsolumbar regions radiating down in the limbs, severe headache, are almost constant. Hyperesthesia is a striking symptom. The least touch or change of position provokes pain. The special sensorium is not infrequently invaded. In every one of my cases there was more or less involvement of the hearing, in five there was impaired vision, although the ocular fundi remained intact. In four of the latter there remained some involvement of the eye muscles, which became paralyzed during one or another recrudescence of the original symptoms accompanied by fever.

In all the ten cases the *sphincters* of the bladder and rectum were involved; during the entire course of the disease incontinence was present, with this difference, however, that during the intervals between the periods of recrudescence, it was less marked. Nevertheless, toward the end, namely, many weeks after the onset, when no more phases of acute symptoms occurred, the incontinence remained unaltered and more and more disturbing.

The psychic status of the patients is characterized particularly by a general intellectual hebetude. The degree of the latter varies from one patient to another and in the same patient at various periods of his disease. They all appeared indifferent, seemingly unable to understand when spoken to. Questions have to be repeated before they show evidence of grasping their meaning. The apathy and indolence may be extreme. The emotional sphere is almost obliterated. When pain is brought on by a change of position, or by a movement of a limb, the facies will not exhibit much suffering. On the other hand, when the same manipulations are made during a period of amelioration of the mental condition, the suffering of the patient is intense. In Cases 3, 5, 7, 8 and 10, there were phases of considerable improvement in the intellectual faculties without a corresponding improvement in the somatic disturbances. Such an improvement may go even as far as to present complete lucidity (in Cases 8 and 10), but the latter is not permanent, and a return to the debilitating status does not fail to take place. In some cases during the periods of recrudescence, namely, when the symptoms become accentuated and present the same picture as during the acute stage, especially when the temperature rises, a delirious state with confusion and incoherence is observed. It disappears when the acute symptoms subside and the patient returns to the chronic course of his malady. In Cases 8 and 10 a mild delirium was observed two and three times, respectively, not during recrudescence of the symptoms, but without a febrile state and when the trophic disturbances became much pronounced. The delirium is then probably due to the state of inanition or exhaustion.

The *course* of the disease in my ten patients was variable. Some of them had more acute attacks than others. The elevation of the temperature during the latter varied also from case to case. The state of prostration which follows the acute attack differed from one patient to another. But what was common to all cases is that the state of mental and physical exhaustion after the individual attacks were more and more profound with each successive attack; also that the course of the disease is very insidious and that, at least in my cases, the termination was fatal. The longest case lasted thirteen months and the briefest two and a half months. In one case (2) the patient died in convulsions which lasted five hours. There was a status épilepticus, as every five minutes a seizure would occur. Patient 1 died suddenly. All others expired after a gradually increasing prostration.

As to the age, my patients were, with two exceptions, all adults. The two cases were children, of 7 and 13 years, respectively. The 13-year-old patient presented no different features from those of the

adults. In the 7-year-old girl the only peculiarity noticed was contracture of the limbs in extension different from that in adults, in whom flexion was the striking feature.

The *pathogenesis* of the chronic form of meningococcus meningitis was not difficult to determine in view of the anatomic findings. Ventricular dilatation with secondary intracranial hypertension; otherwise speaking, a hydrocephalus as a sequel of a meningococcus meningitis is the chief morbid condition. It will readily explain the chronic psychic state which is so conspicuous in the form of meningitis under discussion. Moreover, the trophic disturbances—the sensorimotor manifestations and the state of the sphincters, which all run a chronic course and are so pronounced—are due to the profound degenerative condition of the nerve roots and of the peripheral nerves. Although a recovery is hardly to be expected under such conditions, nevertheless occasionally such recoveries have been recorded.

Diagnosis.—From a diagnostic standpoint difficulties may be encountered, especially when cases fall under observation weeks or months after the onset. First of all, the spinal fluid at this period of the disease is, as we have seen, more or less cytologically mononuclear. Besides, the meningococcus is not to be found directly or culturally. One may think, therefore, of a tuberculous meningitis. In such cases the precipito-reaction of Vincent with tuberculin may be of assistance. On the other hand, the syndrome of intracranial hypertension, especially when visual disturbances are present, will direct us toward cerebral neoplasm. Finally, the subjective and the objective sensory disturbances, together with the motor manifestations, may make one consider polio-encephalitis, polyneuritis or poliomyelitis. The diagnosis must be based on the ensemble of the various individual phases of the disease.

Treatment.—The character of the lesions in the chronic form of meningococcus meningitis precludes the possibility of obtaining results from any form of treatment. In every one of my cases the lumbar punctures were tried for the purpose of injecting antimeningococcus serum. In some cases very small quantities of fluid were obtained; in one case (5) no fluid at all escaped through the needle on several attempts. The serum was injected into the canal at various intervals, but no favorable results were obtained, a fact which I fully anticipated. The pachymeningitis, various adhesions, absence of communication between the cranial and spinal cavities—are all circumstances which, on the one hand, prevented the spinal fluid from escaping sufficiently through the puncturing needle, and, on the other hand, prevented the injected serum from reaching the ventricles, the main seat of the meningococci. Ventricular punctures with injection of serum into

them are therefore directly indicated, but permission could not be obtained for such procedures in my cases. It is to be presumed that when attempts of this character are made during the early phases of the affection, when the tendency to chronicity is first observed, desirable results could be expected. The chronic form of cerebrospinal meningitis is one of the most serious affections. Since it usually follows the acute form which had not been sufficiently treated with anti-meningococcus serum, its recognition is of paramount importance.

1812 Spruce Street.

AN UNUSUAL COMBINATION OF CARDIAC ARRHYTH-
MIAS OF ATRIAL ORIGIN OCCURRING IN A
PATIENT WITH FOCAL INFECTIONS
AND THYROID ADENOMATA*

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AND

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In view of the growing interest in unusual forms of cardiac arrhythmia and their relation to focal infections on the one hand and to thyreopathic disturbances on the other, it has seemed to us worth while to record a case in which remarkable disturbances of cardiac rhythm were encountered in association with (1) peridental, maxillary and tonsillar infection, and (2) minute adenomata of the thyroid gland; and in which marked improvement followed treatment of the infected foci and partial thyroidectomy.

A. CLINICAL HISTORY

ANAMNESIS.—The patient, K. I. N., a salesman, aged 51, married, applied for a general diagnostic study on Feb. 11, 1918.

Family History.—Father died at 90, cause unknown; mother died at 47, at childbirth; one brother, older than the patient, has suffered from a nervous breakdown and has had some thyroid trouble; one sister died of thyroid disease; a second sister has never been robust. Married several years. No children.

Previous History.—Aside from the ordinary diseases of childhood and a severe tonsillitis at 20, the patient has been a singularly robust man—active, energetic, and a hard worker. Through force of circumstances he was compelled to undertake remunerative work at the age of 11 and has been hard at work ever since until the onset of the present illness. Some twelve years prior to admission he met with serious business reverses and after that had to double his efforts to try to recoup his losses. He has never had typhoid, pneumonia, rheumatism nor venereal disease. Aside from a partial tonsillectomy in early life, he has never had any surgical operations. Except for overwork, he has lived fairly hygienically. He is a good walker and has always taken calisthenic exercises at home. Beginning at 25, he has used tobacco moderately, averaging six to eight cigars per day; during the past year he has reduced the amount to three mild cigars a day. He has been almost a total abstainer from alcohol, taking only occasionally a single drink. He states that he has eaten carefully, has not used tea or coffee to excess, and has not resorted habitually to the use of any drug. There is no history of sexual excesses.

*From the Medical Clinic of the Johns Hopkins Hospital.

Present Illness.—Though for the past three or four years he has suffered from insomnia and for more than one year has been somewhat depressed, getting up in the morning feeling worse than on going to bed, he dates the onset of the present illness to an attack nine months prior to admission, supposed to have been "grippe." He ached all over, suffered from shortness of breath, especially on exertion, had an occasional headache without dizziness, and felt weak. His pulse was rapid; he thinks the pulse rate was from 125 to 130 at bedtime. His voice, he says, seemed unnatural. He consulted a physician, who told him that he had "heart disease." He remained under treatment for some four and a half months, though he was not put to bed. He improved somewhat, but did not feel well, and finally was given a course of Nauheim baths, which, he says, made him feel better and reduced his pulse rate to 75 or 80. He still suffers from attacks of fluttering of the heart, with rapid pulse, and complains that his eyes "feel like lead." He remains depressed though there is no reason that he can see for his depression aside from his physical state. He is no longer worried about business matters for his business is now successful. The depression has, however, not been severe, for he has never had weeping spells or any suicidal ideas. He has been having some trouble with his teeth and is under treatment by a dental surgeon.

Physical Examination.—Gait, attitude and posture normal. Fairly well nourished. Height 5 feet 10½ inches. Ideal weight, 167¾ pounds; actual weight, 157¾ pounds stripped. Musculature well developed. Patient is alert and a little apprehensive. The skin is generally a little pigmented; the lips are slightly cyanotic. The superficial veins over the body are slightly dilated and look bluish. The temperature taken over several days varied between 99.3 and 103 F. Pulse rate variable, often 110 or 120. Blood pressure, on first examination, 145 systolic, 80 diastolic.

Head well formed. Acra fairly prominent. Hair abundant and slightly gray. Trace of icteric tint in the conjunctivae. Eyes distinctly prominent. Von Graefe's sign slightly positive. Slight double arcus senilis. Pupils equal; react promptly to light and accommodation. Ears negative. Many teeth have been extracted—all the lower right molars are gone. Gum margins uneven and unhealthy. Lower left molars gone. Upper incisors and bicuspid replaced by bridge. Hearing, sight and smell good. Slight nasal obstruction, more marked on the right than on the left. Tonsils look suspicious. Movements of the face and tongue normal. Speech not disturbed, except that the voice is rather low-pitched and somewhat monotonous.

The neck is a little fuller than normal and there is very marked pulsation of the vessels of the neck, particularly on the right side. The thyroid gland is slightly, but definitely, enlarged, particularly the right lobe. The isthmus is palpable, and the left lobe can also be felt. There is a slightly nodular feel to the thyroid suggestive of minute adenomata. A slight bruit is audible over the right lateral lobe of the thyroid. No tracheal tug. No cervical rib. No enlargement of the lymph glands of the neck. Movements of cervical spine normal.

Thorax is well formed, symmetrical; expansion good, equal on the two sides. Epigastric angle wide. There is a dilated vein running over the upper right chest, not visible on the left. Percussion sounds normal over the lungs. Breath sounds normal over both fronts and backs. There is rather marked cyanosis of the face and hands and a little clubbing of the finger tips.

The apex beat of the heart is in the fifth space, just lateral from the mamillary line. There is some increase of retrosternal dullness. The left chest is shaken a little with each heart beat. No thrill felt over the heart though the shocks of both the first and second sound can be readily felt at the apex. On auscultation there is tachycardia and a tendency to pendulum rhythm, but no heart murmurs are heard. The heart rate is about the same lying as standing. The heart is obviously a little enlarged on percussion. The abdomen is symmetrical. The spleen is not palpable. The edge of the liver can be just felt below the costal margin at the end of deep inspiration. No

hernia. No abnormal masses palpable in the abdomen. No tenderness over the appendix or over the gallbladder. Rectal examination negative. Left testicle undescended. Sensation normal. No paralyses. Reflexes normal.

LABORATORY TESTS

Blood Examination: Red blood corpuscles, 5,120,000; hemoglobin, 100 per cent.; white blood corpuscles, 9,400.

	Number	Per Cent.
Polymorphonuclears	175	70.0
Eosinophils	1	0.4
Basophils	0	0.0
Small mononuclears	65	26.0
Large mononuclears }	9	3.6
Transitionals		
	<hr/> 250	<hr/> 100.0

Red blood corpuscles and platelets normal. No abnormal cells seen.

Blood Wassermann Reaction: Antigen A—Cholesterinized human heart—negative. Antigen B—Acetone insoluble lipoids—negative. Antigen C—Plain extract beef heart—negative.

Gastric Analysis.—Thirty c.c. recovered; colorless; free hydrochloric acid, 20; combined acid, 48; total acidity, 68.

Occult blood, 0; lactic acid, 0; microscopically negative.

Stool.—Brown, formed; bile, plus; occult blood, guaiac, 0; benzidin, 0; microscopically negative.

Urine.—Specific gravity, night and day, 1.024 and 1.020, respectively; albumin, faint trace; sugar, none. Microscopically: Moderate number of white and red blood corpuscles. No casts.

ROENTGEN-RAY EXAMINATIONS

Roentgenoscopic of Chest.—Heart somewhat enlarged, lying transversely; diffuse dilatation of aorta; no sacculation; good pulsation throughout. Slight anterior encroachment on retrocardiac space in its inferior portion.

Impression: Diffuse, moderate dilatation of aorta; slight enlargement of the heart.

Roentgenoscopic of Gastro-Intestinal Tract.—Cowhorn, hypertonic stomach; peristaltic waves slightly increased in depth and frequency; duodenal cap not visualized. Flexibility good and mobility normal; no filling defects; pyloric extremity in apposition with hepatic flexure but separable from it by palpation. Hepatic flexure at level of iliac crests; transverse and descending colon negative.

Serial Roentgenograms of Gastro-Intestinal Tract.—Hypertonic, cowhorn stomach in good position; no filling defects; rapid emptying; no six hour retention. Colon in good position; marked cecal stasis.

Roentgenogram of Paranasal Sinuses.—There is very slight clouding of the right antrum; otherwise the paranasal sinuses are negative.

Roentgenogram of Lungs.—The upper thirds of both lungs show some slight clouding, especially in the apical regions. Probably old, inactive tuberculous process.

Teleroentgenogram.—

M. R. (=maximal distance from median line to right margin of heart).. 6.7
 M. L. (=maximal distance from median line to left margin of heart).... 9.1
 L. (=length of heart shadow).....16.5
 Br. (=breadth of heart shadow).....11.9

The heart is rather large both on the right and on the left. It lies slightly transversely. The aortic knuckle is a little dilated. There is some mediastinitis both on the right and on the left, more marked on the right. There are increased shadows due to calcified glands at the roots of both lungs. The bases are both slightly cloudy.

Roentgenogram of Sella Turcica.—No definite outline of the sella is visible.

Roentgenogram of Clavicular Regions.—This gives no evidence of cervical rib; no unusual substernal shadows.

SPECIAL TESTS

Epinephrin Test.—

Time	Pulse	Blood Pressure	
10:35	124	140/85	Dyspnea from climbing stairs; slight tremor of fingers; hands dry.
10:45	104	135/85	Dyspnea much less; pulse slower; quite regular; tremor +; slight moisture of hands.
10:47	Epinephrin, 0.5 c.c., hypodermically.
10:49	104	133/80	Tremor +; slight moisture of hands.
10:55	112	125/75	Definite increase of tremor; hands moist.
11:00	112	125/75	Marked tremor; hands moist.
11:05	112	128/80	Marked tremor; hands moist.
11:12	112	130/80	Marked tremor; hands moist.
11:20	108	125/75	Marked tremor; hands moist.
11:35	108	123/70	Marked tremor; hands moist.
11:45	112	126/70	Marked tremor; hands moist.
11:55	108	120/65	Still marked tremor; hands moist; slight arrhythmia.
12:05	112	123/70	Still marked tremor; hands moist; slight arrhythmia.
12:10	150 (?)	120/70	Patient sits up quietly; pulse almost uncountable; marked irregularity in force and rhythm; "palpitation"; marked tremor.
12:15	96	140/80	Still in sitting posture; very little palpitation; tremor well marked. Says "heart often acts that way."

Impression: The marked increase in tremor of the hands, increase in pulse rate and perspiration would indicate some epinephrin hypersensitiveness; the late appearing palpitation with arrhythmia and tachycardia may also be further proof.

Dental Report.—Examination shows an osteomyelitis of the superior maxillary bones, extending to the buccal wall of the sinus. There is also an indurative gingivitis.

Rhinologist's Report.—There is a very definite chronic infection of the tonsils, particularly the left. Both tonsils have been partially removed. Hypertrophied lymphoid tissue in nasopharynx. The nasal septum is deflected, causing obstruction on the right side of the nose.

The right antrum is dark on transillumination. Would advise roentgenogram of sinuses.

In nasal examination no definite evidence of any infection of the sinuses can be made out. No polypi. No discharge to be seen.

Psychiatrist's Report.—A very searching examination of the patient reveals practically nothing but too limited a mental diet, with continuous work, without any recreative interests, a rather shut-in family tendency and at present an impossibility of getting the exercises on which he used to depend—hunting, horseback riding, walking, etc. The patient knows no games; he dislikes the theater; he is not interested in being with other people; he does not read. He has led a very careful life, training himself with physical exercises.

The exceedingly quick tremor and the steady high pulse are very suggestive of hyperthyroidism. There is no evidence of overstimulation or of anxiety neurosis. The whole picture suggests much more an excessive grind without let-up and hobbies and the necessary lubrication in a man naturally somewhat tense and nervous. I should expect most relief from a readjustment of his life, which would permit of more adequate recreation after his probable hyperthyroidism is adjusted.

Urologist's Report.—The patient voided 4 ounces of perfectly normal looking urine. Penis normal. There is only one testicle in the scrotum, the right one, and that is perfectly normal. The left testicle can be felt as a small body in the inguinal canal; it shows marked atrophy. The left side of the scrotum is also not developed.

Anal splineter good. The prostate is distinctly enlarged, generally smooth, elastic. The seminal vesicles are palpable, slightly distended, but soft. One gets the impression, on rectal examination, of a moderate amount of benign prostatic hypertrophy. A catheter was passed with ease and there is no residual urine.

Impression: There seems to be no indication for cystoscopy, and the patient is having no obstructive symptoms. There is present a slight grade of benign prostatic hypertrophy not producing symptoms. No indication for treatment.

Heart Station Report.—(See special electrocardiographic studies later.) As the first electrocardiographic examination revealed very interesting findings the patient was taken into the private ward at the Johns Hopkins Hospital for a period of observation and special study at the Heart Station, as it seemed worth while to analyze very carefully the peculiar cardiac arrhythmia existing.

Clinical Diagnosis.—1. Remarkable, probably unique, form of cardiac arrhythmia (to be further analyzed).

2. Graves' syndrome, including tachycardia, struma, tremor, protrusio bulborum and slight hypersensitiveness to epinephrin.

3. Chronic tonsillitis and antritis on the right side.

4. Oral sepsis.

5. Slight atherosclerosis with dilatation of the aorta, enlargement of the heart, double arcus senilis and slight nephropathy.

6. Cecal stasis, hyperacidity, and palpable liver.

7. Undescended left testicle and slight benign prostatic hypertrophy.

8. Psychoneurotic state with insomnia, depression and disturbance of the somatopsychic.

Treatment.—Feb. 20, 1918, the patient was admitted to the private ward of the Johns Hopkins Hospital for further observation and for treatment. He was kept at rest in bed and on a light diet and was given massage three times a week. His dentist treated the gingivitis. The infected antrum was irrigated. April 18 the infected tonsils and adenoids were removed by the rhinologist. April 26, 1918, he was transferred to the surgical side for the removal of a portion of his thyroid gland by Dr. Emil Goettsch. He returned to the medical service April 30, 1918, and remained for further observation and medical treatment until May 10, 1918, when he was discharged from the hospital, very much improved.

May 15, 1918, he reported that he was very much better. His own impression was that the thyroid operation had helped him more than the treatment of the teeth or the removal of the tonsils. On being asked of what his improvement consisted, he said: "I feel more like I used to feel. I feel that I am getting to be all right. I can take an interest in things. I am no longer despondent. My appetite is better. I am not nervous now. Even though I don't sleep as well as I should like to sleep, I do not feel nervous. My voice is better though I am still weak. In every way I feel better." His pulse rate was 78 and regular. The fine tremor was still pronounced in the fingers. The eye signs were still present. The weight was about normal.

The patient was seen again June 24, 1918. He said that he has been getting on well; that he has had no more fluttering of his heart, though he feels an occasional dropped beat. He no longer has headaches. He eats naturally and looks and feels very well, weighing 174 dressed. He takes calisthenic exercises, walks an hour each day, and has been attending to his business, though he has been careful to avoid overexertion and mental fatigue. His pulse rate is now about 100 and is regular except for an extrasystole at about every sixtieth beat.

B. ELECTROCARDIOGRAPHIC STUDIES

DR. H. B. RICHARDSON

Electrocardiograms were taken at frequent intervals. Williams' model of the Einthoven string galvanometer made by Hindle & Co., was used. The fiber was of gilded quartz and had a resistance of 3,600 ohms. The resistance of the patient to a direct current varied from 1,500 to 3,100 ohms. In all records the tension of the string was so adjusted that a difference of potential of 1 millivolt caused a deflection of 1 centimeter. This standardization is shown graphically in Figure 4. The standardization was similarly recorded and verified in each lead in all records. The string was aperiodic in all cases. In the records, abscissae equal 0.1 millivolts, ordinates 0.04 second.

VIEWS OF VARIOUS OBSERVERS REGARDING ABNORMALITIES OF THE P-WAVE

As this study is concerned mainly with the disturbances of atrial function met with in a single patient, a brief review of the literature on the abnormalities of form of the P-wave may be of interest.

In general, according to Einthoven, Fahr and de Waart,¹ an inverted wave occurring at the same instant of the cardiac cycle in all three leads means negativity at the basal region. Specifically, an inverted P-wave in all three leads means onset of negativity at a point opposite from the normal; that is to say, low in the atrium instead of in the sino-atrial node. Lewis² has shown experimentally that stimulation of the atrium yields a P-wave the form of which varies according to the location of the stimulus; if near the sino-atrial node it is of normal contour; if in midatrium it tends to be iso-electric; if in the atrium it is inverted. In paroxysmal tachycardia, the P-wave is usually inverted and the stimulus is therefore held to originate low in the atrium. In atrial flutter the P-wave is almost invariably abnormal.

1. Einthoven, W., Fahr, G., and de Waart, A.: Ueber die Richtung und die manifeste Grosse der Potentialschwankungen im menschlichen Herzen über den Einfluss der Herzlage auf die Form des Elektrokardiogramms, *Arch. f. d. ges. Physiol.* **150**:275, 1913.

2. Lewis, T.: Galvanometric Curves Yielded by Cardiac Beats Generated in Various Areas of the Auricular Musculature. *The Pacemaker of the Heart*, *Heart* **2**:23, 3 pl., 1910-1911.

Recently Heard and Strauss³ concluded from the study of a case that it is diphasic, primarily downward, and that "the origin of the auricular impulses is believed to be ectopic."

In atrioventricular rhythm, the P-wave is frequently, though by no means constantly, inverted. As an example of this, the observations of Williams and James⁴ may be mentioned. In heart block, cases have been observed in which the P-wave that falls in the ventricular cycle is both premature and inverted (Cohn and Fraser,⁵ Wilson and Robinson⁶). In *situs inversus*, of course, the P-wave is inverted in Lead I, owing to the position of the heart. Apart from these conditions, inversion of the P-wave in all three leads is exceedingly rare. Goddard⁷ found among 700 records but one instance of inversion of the P-wave, and in this case the inversion was transient and confined to Lead I. In personal observation of some 400 records, we have seen it only in this case.

Hart⁸ publishes, on page 73 of his monograph, a curve of Lead II in which the P-wave is inverted. The explanation of his figure reads: "Every P-wave is of an abnormal form, indicating an abnormal point of origin in the auricle, or an abnormal path through the auricular wall." No discussion is given in the text.

Apart from the conditions mentioned, then, inversion of the P-wave in all three leads is exceedingly rare, and indicates that the excitation wave originates low in the atrium.

INTERPRETATION OF RECORDS

For the sake of clearness, the records will be discussed in an arbitrary rather than in a chronological order. Those in which the ventricles beat regularly will be considered first. In Figures 1, 2 and 3, three different mechanisms are shown. In Figure 1 the rhythm is regular, the rate 112, the sequence left ventricular, and the P-R interval is 0.20 second in Lead II. The P-wave is upright in all three leads. T is primarily downward in Leads I and II, and has a suggestion of a

3. Heard, J. D., and Strauss, A. E.: Auricular Flutter. A Consideration of Some Problems Arising in the Study of a Case of the Literature, Arch. Int. Med. 20:409, 1917.

4. Williams, H. B., and James, H.: Reversal of the Cardiac Mechanism, Heart 5:109, 2 pl., 1913-1914.

5. Cohn, A. E., and Fraser, F. R.: The Occurrence of Auricular Contractions in a Case of Incomplete and Complete Heart Block Due to Stimuli Received from the Contracting Ventricles, Heart 5:141, 1 pl., 1913-1914.

6. Wilson, F. N., and Robinson, G. C.: Heart Block. I. Two Cases of Complete Heart Block Showing Unusual Features, Archives Int. Med. 21:166, 1918.

7. Goddard, C. H.: Changes in the P-Wave of the Human Electrocardiogram, Archives Int. Med. 16:633, 1915.

8. Hart, T. S.: The Diagnosis of Abnormalities of Myocardial Function, Arch. Diagnosis 9:31, 1916.

diphasic character. Its excursion is not over 0.25 millivolt in any lead, and it consists only of a slight, smooth undulation in Lead III. These records constituted the nearest approach of the patient to a normal rhythm. The mechanism may, therefore, be referred to as the physiologic rhythm, although distinct abnormalities are shown; that is, predominance of the left ventricle, tachycardia, a slight increase of the conduction time, and an inversion of the T-wave.

Figure 2 shows pronounced alterations. P is slightly diphasic, but chiefly upright in Lead I. It is notched in Lead II and the second portion, that which follows the notch, is not so high as that which precedes it. In Lead III the notch persists and the two components of the wave are of equal height. The change in the contour of the P-waves indicates that the origin or course of the excitation wave in the atrium is different from that of the physiologic rhythm. The most striking part of the record is, however, the alteration in the form of the wave at the beginning of T. Here in all three leads is seen a small deflection, which is absent from the physiologic rhythm of Figure 1. In each lead the contour of this wave is the same as that of P. It represents, therefore, an accessory atrial contraction.

The same reasoning is applicable to Figure 3. The deflection occupying the position of T is much deeper than in Figure 1. The increase of depth may be ascribed to a combination of an accessory atrial wave and the T-wave. To produce this effect, the accessory contraction, which may be conveniently labeled P', must be inverted. This P' is inverted in all three leads. The same is true of P. The curve therefore shows inverted P-waves and inverted accessory atrial waves, which fall in the early portion of the T-waves. The mechanism is the same as in Figure 2, except that the waves under discussion are inverted. For the reasons indicated in discussing the literature, this inversion indicates that the excitation wave begins low in the atrium.

Against the above interpretation is the possibility that the change in form of the T-wave is due not to a superimposed wave, but to a change in the T-wave itself. The transition shown in Figure 4 tends to dispose of this objection. At the beginning, the entire curve was displaced by a potential difference of one millivolt, for the purpose of recording the sensitiveness of the string; nevertheless, the contour of the waves remains clear. The first two T-waves are of small amplitude, diphasic and primarily downward; subsequent waves show a gradually increasing, sharp downward depression. Unless the T-wave is assumed to change its shape in four beats without change in rate or modification in the contour of other waves, the depression must be due to a superimposed atrial contraction. While these P-waves are developing, the P-wave changes from a slight upward undulation to a frankly inverted wave. This curve shows a transition from a relatively

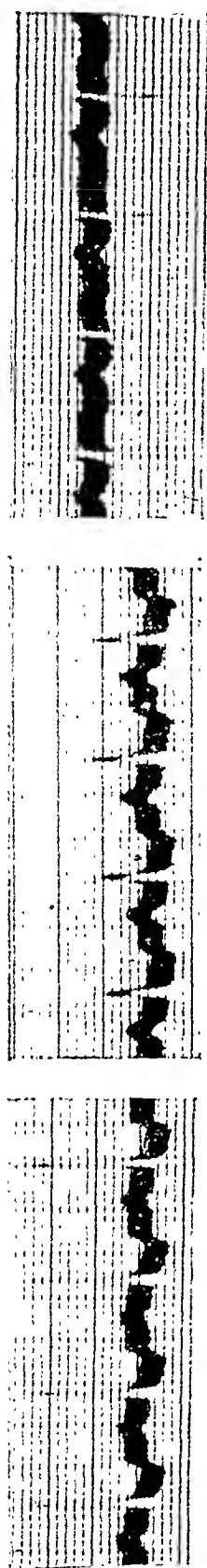


Fig. 1.—March 28, 1918. Physiologic rhythm.

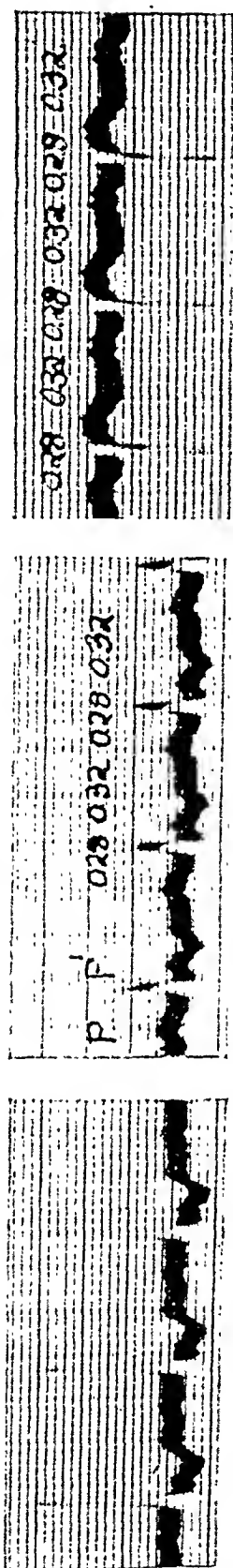


Fig. 2.—Feb. 15, 1918. P-wave notched. Blocked alternate atrial extra-systoles.

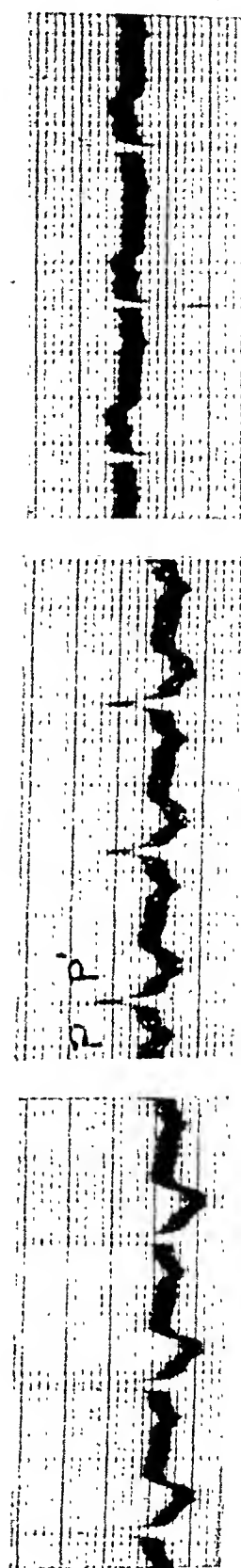


Fig. 3.—March 16, 1918. P-wave inverted. Blocked alternate atrial extra-systoles.

normal rhythm to one in which the excitation wave begins at a point low in the atrium, and in which an accessory contraction of the atrium occurs during systole of the ventricle.

Three possibilities suggest themselves as explanation for the appearance of this wave. The first of these is atrial flutter with a 2:1 atrioventricular block. In flutter, as ordinarily understood, the atrial waves are regular. A glance at Figures 2 and 3 is sufficient to show that this is not the case in the present instance. The accessory atrial contraction occurs prematurely. If it be designated as P', then in Leads II and III of Figure 2, in which the waves offer the most definite points for measurement, the P-P' interval measures 0.28 second, whereas, the P-P interval measures 0.32 second. These figures are identical in each of five cycles. In none of the electrocardiograms of the eleven cases of flutter on file in our records is there an instance of such an arrhythmia, nor have we encountered it in any of the published electrocardiograms of flutter. A tracing obtained from this

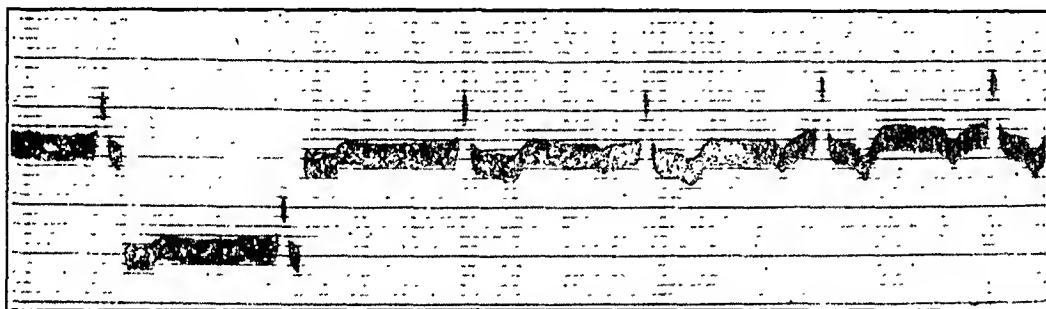


Fig. 4.—March 6, 1918. Showing transition from physiologic rhythm to alternate blocked atrial extrasystoles.

patient at another time demonstrated atrial flutter and differed radically from the one under discussion (Fig. 7). Atrial flutter, as ordinarily understood, may therefore be excluded.

Another possibility is the retrograde stimulus of the atrium by the contracting ventricle, either by a retrograde excitation wave or by a mechanical stimulus. The former mechanism⁴ has been recorded in atrioventricular rhythm, the latter in complete heart-block,^{5, 6} that is to say, in rhythms in which the ventricle is the pacemaker. Neither has been observed, as far as we are aware, in the course of a sequential rhythm. A third possibility is that the P'-waves are due to atrial extrasystoles that evoke no ventricular response. They occur so early that a fatigue block is readily conceivable, especially in view of the slightly prolonged P-R interval of 0.20 second. Additional tracings were required to decide between the last two alternatives.

An example of these is shown in Figure 5. In Lead II the first two cycles indicate the same mechanism as Figure 3; that is, an abnormal path of the excitation wave in the atrium and accessory atrial

contractions. The third ventricular complex is premature. It follows 0.28 second after P' without an intervening P. Evidently this ventricular complex is a response to the atrial contraction P' , the diminished conductivity being explained by the fatigue caused by the short diastole. This P' becomes P also, and the expected P-wave falls in the ventricular cycle, thus becoming what has been called an accessory atrial contraction. After this change of step the mechanism proceeds as before. Three similar ventricular responses are shown in Lead I and one in Lead III; in these instances the P' -R interval is 0.24 second, which is not much greater than normal. The accessory atrial waves that fall in ventricular systole are thus capable themselves of eliciting

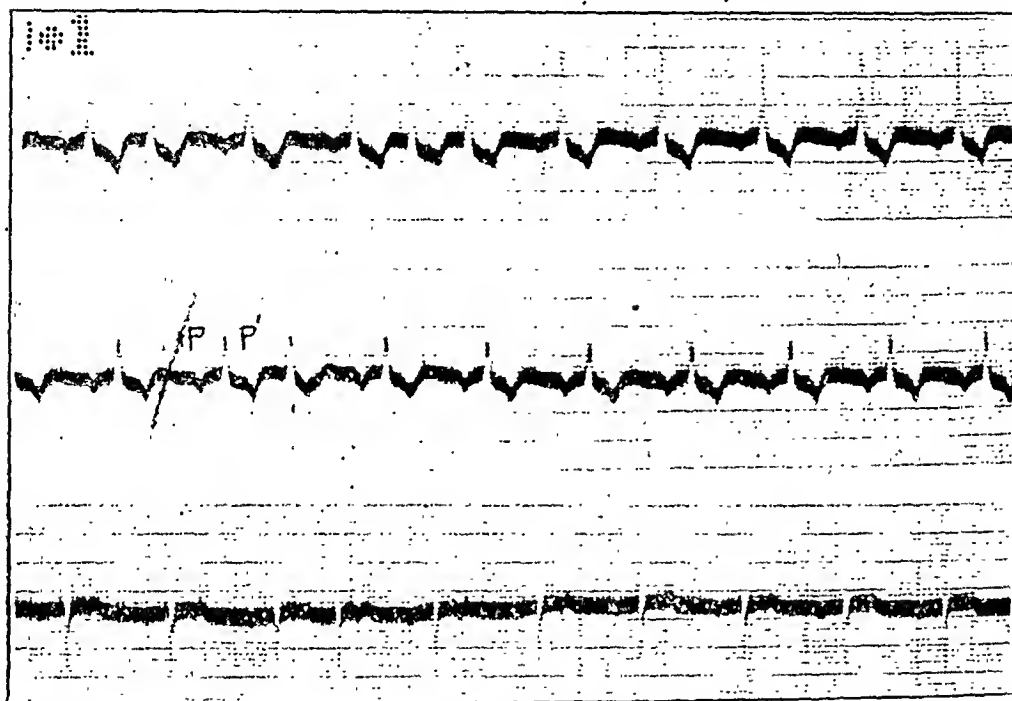


Fig. 5.—March 6, 1918. Inverted P-wave. Alternate atrial extrasystoles, usually blocked, sometimes not blocked.

a ventricular response. Thus the mechanism is alternate atrial extrasystoles of the same origin or path as the sequential atrial waves, or what might be termed an atrial pulsus bigeminus. These extrasystoles are usually blocked but often provoke a ventricular response, though after an interval that is somewhat greater than normal. Attempts to explain the mechanism on the basis of a stimulus passing backward from ventricle to atrium become very involved.

In Figure 6 is shown essentially the same mechanism, with the exception that more of the atrial waves are followed by a ventricular response. When this occurs several times in succession it constitutes a short paroxysm of tachycardia in which the rhythm is regular. The

figure begins with four such beats; then comes a pause, a cycle of the rhythm of Figure 3, and then a relatively normal P-wave followed by a paroxysm of seven rapid beats. The R-R intervals indicated on the figure show that the rapid rhythm is regular except for the last interval, which is a trifle shorter. The portion of the curve that lies between the R-waves varies in contour, but the P-waves are discernible. After this short run of tachycardia the mechanism of blocked alternate atrial extrasystoles is resumed.

Still another mechanism is shown in Figure 7. It is perhaps well to recall that during the physiologic rhythm of Figure 1 the T-wave in Lead II consisted only of slight undulation. In Lead III of Figure 7 there is a series of regular waves between each two ventricular beats. These waves are seen to be continuous throughout the systole and diastole, though they are modified in shape when mixed with the ventricular complexes. The curve is a definite picture of atrial flutter at an atrial rate of 300. The ventricle responds usually to every fourth, occasionally to every third, atrial contraction. In Lead I the same mechanism is in evidence, though it is less characteristic. In Lead II, however, the mechanism is not the same. The record differs in no

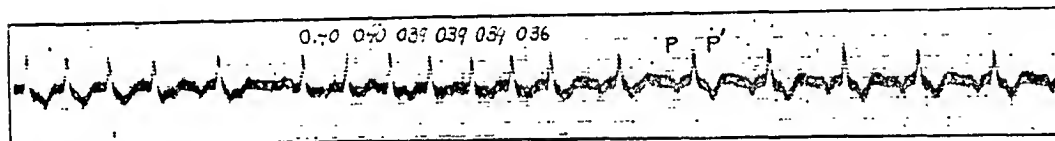


Fig. 6.—March 14, 1918. Two short paroxysms of tachycardia with regular rhythm. Reversion to blocked alternate atrial extrasystoles.

essential from that in Figure 3. Two inverted P-waves and two only are distinguishable in the cardiac cycle, one in the normal position and one, definitely premature, fused with the T-wave. Although both these waves are pronounced, no intermediate atrial waves can be seen. The mechanism is evidently different from that of the other leads and consists of inverted P-waves and blocked alternate atrial extrasystoles. As the leads were taken in chronological order, the change of mechanism during the shift from Lead I to Lead II and back again during the shift from Lead II to Lead III is something of a coincidence, yet the records seem to permit of no other interpretation.

OBSERVATIONS ON COMPRESSION OF THE VAGUS

The vagus was stimulated by digital compression of either or both nerves over the carotid artery in the neck. Continuous electrocardiograms were taken, including the period of compression and a few beats before and after. The rate before vagus pressure was compared with that during the four or five beats that included the release of pressure.

Results varied according to the mechanism present. The effect on the physiologic rhythm was recorded on four occasions, as follows:

ATRIAL RATE		
	Before	At Release
Right vagus.....	83	64
Right vagus.....	111	104
Left vagus.....	82	71
Left vagus.....	107	104
Both vagi.....	107	96
Both vagi.....	112	107
Average	100.4	91.0

Thus marked slowing resulted.

On the mechanism of blocked alternate atrial extrasystoles, with P-wave upright but abnormal (Fig. 2), one observation was made.

ATRIAL RATE	
Before.....	96
At Release.....	96

Here no change resulted.

On the mechanism that resembled the preceding except that the P-wave was inverted and that not all the extrasystoles were blocked (Figs. 3, 5 and 6), observations were made on three occasions, as follows:

ATRIAL RATE		
	Before	At Release
Right vagus.....	141	140
Right vagus.....	103	105
Left vagus.....	140	138
Left vagus.....	165	168
Both vagi.....	160	163
Average	141.8	142.8

Here no change resulted.

On atrial flutter one observation was made.

ATRIAL RATE		
	Before	At Release
Right vagus.....	300	300

Thus no change resulted.

The average of all observations on subnormal atrial mechanism was:

ATRIAL RATE	
Before.....	157.9
On Release.....	158.6

In no instance did vagus pressure produce any change of mechanism except that it tended to prevent ventricular response to atrial extrasystoles. Examples of vagus pressure on physiologic and abnormal mechanisms are shown in Figure 8.

Thus, pressure on the vagus nerves caused a marked reduction in atrial rate during the physiologic rhythm and no change during the activity of an abnormal atrial mechanism. The observations have been described in detail because they have a bearing on the latter. The inversion of atrial waves might be ascribed either to a dislocation of the pacemaker or to an abnormal path of the excitation wave in the atrium analogous to that which occurs in the ventricle when there is a defect in the Purkinje system. If the latter alternative be correct, and the impulse arise in the sinus node, it is to be expected that pressure on the vagus would reduce the atrial rate to the same degree as occurs during the physiologic rhythm. That this does not take place is evi-

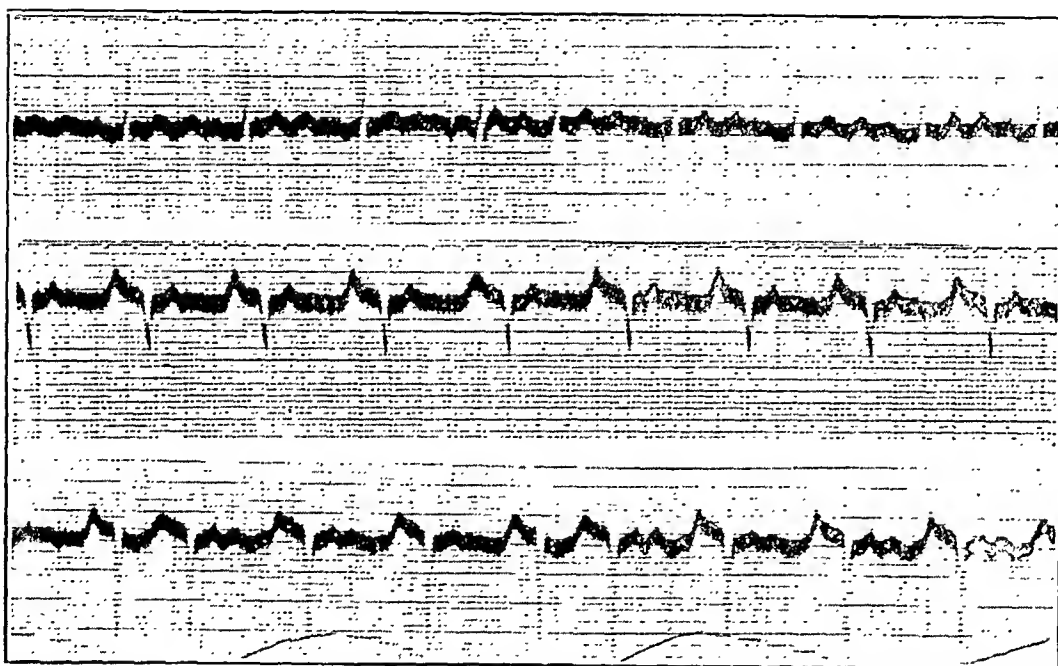


Fig. 7.—March 4, 1918. Atrial flutter. Inverted P- wave. Blocked alternate atrial extrasystoles.

dence that in the abnormal rhythm the pacemaker is dislocated. This case would seem to offer no support for the view that there is in the atrium, as in the ventricle, a specialized tissue subject to damage, which conducts the excitation wave, as concluded by Eyster and Meek,⁹ and recently contested by Lewis.¹⁰

The failure of pressure on the vagus to produce any radical change of mechanism is evidence that in causing the dislocation of the pacemaker the vagus plays no part.

9. Eyster, J. A. E.: Experiments on the Origin and Propagation of the Impulse in the Heart, *Heart* 5:119, 137, 3 pl., 1913-1914.

10. Lewis, T., White, P. D., and Meakins, J.: The Susceptible Region in A-V Conduction, *Heart* 5:289, 1913-1914.

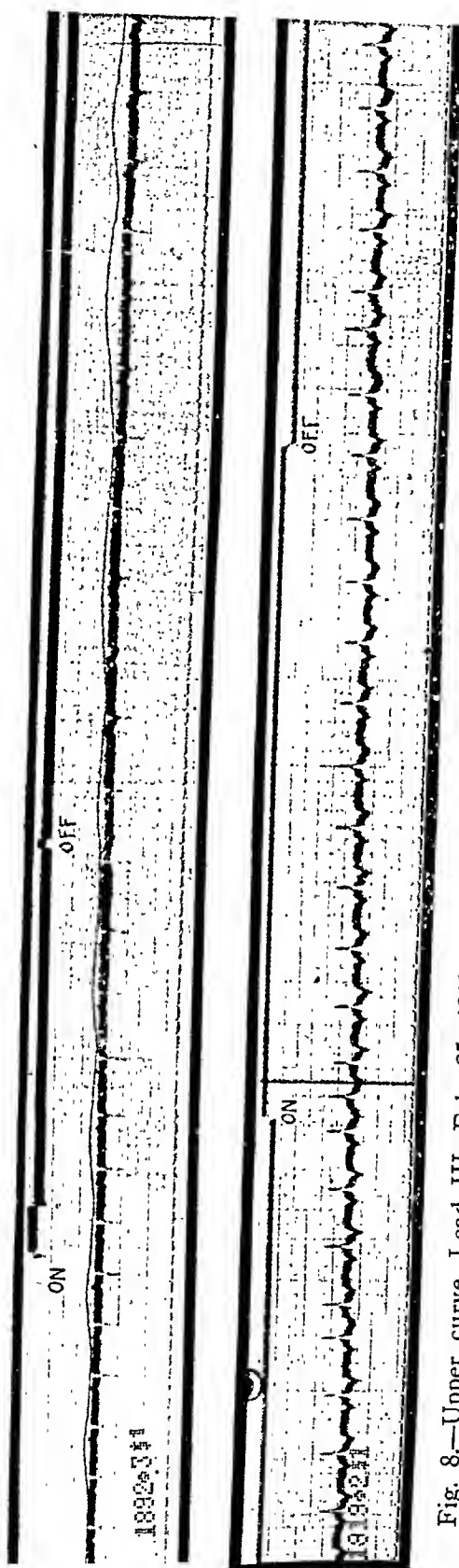


Fig. 8.—Upper curve, Lead III, Feb. 25, 1918. Effect of pressure on right vagus on physiologic rhythm. Lower curve, Lead II, March 11, 1918. Effect of pressure on right vagus on abnormal rhythm.

OBSERVATION ON EFFECT OF ATROPIN

One observation was made on the effect of atropin; $\frac{1}{60}$ grain of the sulphate was injected subcutaneously. Curves taken five minutes before showed the physiologic rhythm and a slowing of ventricular rate by pressure on both vagi from 105 to 99. Curves were taken at 5-minute intervals for 45 minutes. The effect of atropin was demonstrated by the symptom of dryness of the mouth and by the fact that vagus pressure one-half hour afterward had no effect on the rate. Although the drug had thus a well marked effect and increased the rate from 105 to 130, it produced no change in the mechanism. Depression of the vagi by atropin, like stimulation of them by pressure, failed to produce a change of mechanism. No evidence was obtained that the abnormal mechanism is related to vagus tone.

SUMMARY OF ELECTROCARDIOGRAPHIC STUDY

If the above interpretations are correct, we have observed in this patient at one time or another the following:

1. Physiological rhythm.
2. Dislocation of the pacemaker from the sino-atrial node to points elsewhere in the atrium.
3. Alternate atrial extra-systoles, none of which provokes a ventricular response.
4. Alternate atrial extrasystoles, many of which provoke a ventricular response.
5. Paroxysmal tachycardia.
6. Atrial flutter.

It is hoped that the very unusual combination of atrial disturbances presented by this case may be welcomed by those who desire to throw light on abnormal functioning of the atrium of the heart.

PITUITARY HEADACHES AND THEIR CURE*

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Headache as a symptom is well known to all. The patient who complains of it is too often given a cathartic and aspirin and dismissed without adequate study to determine its true etiology. He may then go elsewhere and return after he has developed more definite signs. I remember one patient who returned four days later with the complete picture of a tuberculous meningitis.

Headache commonly presents itself to us as the symptom of some systemic disease, such as circulatory disturbance, especially hypertension, nephritis, anemia, an acute febrile disease, or poisoning by various toxic substances. These may be exogenous or endogenous; for example, lead, carbon monoxid, alcohol, or the toxins resulting from acidosis, diabetes, uremia, or from the gastro-intestinal tract. Syphilis is a frequent cause of headache. There are likewise local causes in disturbances of the cerebral circulation, a myositis of the occipitofrontalis muscle, periostitis or gumma of the cranium, inflammation of the accessory sinuses, increased intracranial tension resulting from abscess, meningitis, tumors, etc., errors of refraction and eye-strain, or migraine which may prove to be an intermittent claudication of the cerebral arteries. Certain headaches are of reflex origin, as those which come from menstrual irregularities or pelvic disease. Headache may be a symptom of hysteria and the various neuroses and psychoses. So much for the multitudinous causes to which we often ascribe this distressing symptom.

The part which the pituitary gland may play in the production of headache is frequently overlooked. The clinical picture of severe frontal headache, somnolence, mental dulness, polyuria, increased sugar tolerance or glycosuria, oculomotor palsies, bitemporal hemianopsia, and evidence of disturbed bony metabolism or adiposity, sexual regression, etc., is a well known syndrome caused by pituitary tumors. But it is the early and less easily recognized pituitary disturbances on which interest must center, for that is the stage in which therapy will help; and one of the first symptoms of a pituitary gland which is functioning improperly is a frontal headache which does not yield to the usual remedies.

* From the Third Division of the Neurological Institute.

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to present in all its phases, knowledge of the therapeutic method at the end will show

usually, an enlargement of the demand made on it, or a more common in women than in men it is most frequently seen

any of the pituitary gland is of the brain, connected to it by the infundibular process, and lying within the confines of the sella turcica, a bony cavity whose physical limitations it is subject. The size of the hypophysis is quoted by various authors,¹ averaging in the sagittal plane from 6 to 10 mm., vertical from 10 to 14.5 mm., transverse from 5 to 9.75 mm., the weight 0.6 gm., comparing favorably in size to the hazel nut. The gland, made up of three parts, is surrounded by a thin capsule—a continuation of the dura mater; anterior to it lie the olivary eminence and the anterior clinoid processes; below, the dorsum sellae; behind, the posterior clinoid processes; and above, overhanging the entrance to the sella in the form of a diaphragm, is a firm prolongation of the dura which is perforated by the infundibular process. The nerve supply is derived from sympathetic plexuses along the carotid artery. Tilney,² in an admirable article, has contributed largely to the phylogenesis and anatomy of the hypophysis. To Cushing³ and Falta⁴ we owe important contributions to its physiology and clinical significance.

From the foregoing it can be seen that the pituitary gland is entirely surrounded by a firm framework, on three sides by bone, above by dura and only on the lateral aspect is there any opportunity for expansion. If the gland were situated in masses of loose areolar tissue such as the thyroid or the adrenals, a considerable enlargement would be possible before pressure symptoms were felt or could even be detected; but, let the hypophysis enlarge just 2 or 3 mm., and there will develop

1. Zander: Quoted by Munson and Shaw, *Archives Int. Med.* **14**:493, 1894. Hitchcock: *Med. Rec.*, New York, Sept. 10, 1911.

2. Tilney: Pituitary gland. *Mem. Wistar Inst.*, 1911.

3. Cushing, H.: *Pituitary Gland and Its Disorders*, 1912.

4. Falta: *Ductless Glandular Diseases*.

a train of symptoms dependent on this mechanical discrepancy. We see, then, that there are two factors which enter into the production of these headaches, the size of the sella turcica and the size and pathologic condition of the pituitary gland.

In a series of twelve cases showing no dyspituitary signs or symptoms, normal sella turcica measurements are shown in Table 1.

TABLE 1.—NORMAL SELLA MEASUREMENTS AS DETERMINED BY THE AUTHOR

Name	Antero-posterior	Depth	Name	Antero-posterior	Depth
A	11	10	F	10	8
D	11	10	S	11	7
B	12	10	M	11	9
M	10	8	E	11	10
P	10	8	H	11	8
A	9	8	M	11	10
Average	9-12	7-10			

Average measurements quoted by other writers are as shown in Table 2.

TABLE 2.—MEASUREMENTS OF SELLA NOTED BY VARIOUS OBSERVERS

Name	Anteroposterior	Depth
Keith ⁵	10-12	8
Potts ⁶	8-13	6-10
Fearsides ⁷	10-12	8

To compare with the foregoing a series of fifteen cases which showed distinct dyspituitary signs, Table 3 reveals either an enlargement of the sella or else a definite contraction:

TABLE 3.—COMPARISON OF CASES SHOWING DYSPITUITARY SIGNS

Name	Antero-posterior	Depth	Name	Antero-posterior	Depth
D. S.	12	9	R. W.	17	13
E. H.	11	11	S. F.	9	8
J. T.*	15	11	E. M.†	30	30
E. F.	14	12	D. S.*	12	8
S. J.	11	8	W. G.*	9	7
E. W.*	12	12	N. C.*	15	13
S. W.	12	10	N. F.*	15	8
J. L.	13	12	M. B.*	5	5

* Cases marked with * are measurements of sellae of case reports.

† E. M. is a case of pituitary tumor with acromegaly.

Another table will serve to show the comparative measurements of the normal hypophysis and the sella turcica (Table 4):

TABLE 4.—COMPARATIVE MEASUREMENTS OF NORMAL HYPOPHYSIS AND SELLA

	Sella-Turcica	Hypophysis
Anteroposterior	9-12	6-10
Vertical	10-14	7-10

5. Keith: Lancet, London, 1911, 1, 993.

6. Potts: Jour. Am. Med. Assn., 1913, 61, 1188.

7. Fearsides: Lancet, London, 1914, 2, 16.

From these figures and facts we determine that normal pituitary glands usually have normal sella conformation, but should the glandular function be disturbed there will result certain signs and symptoms and the roentgenogram will show an abnormal sella turcica.

Roentgenograms of this type of case having "pituitary" headaches and dyspituitary signs reveal a wide variety of sellae turcicae and I should like to note here the importance of a careful study of each plate by the clinician with a standard normal plate as reference. There may be a very small contracted fossa with clinoids in apposition, or there may be a large fossa with a similar formation of clinoid processes; the former of these would be expected to show hypopituitary and the

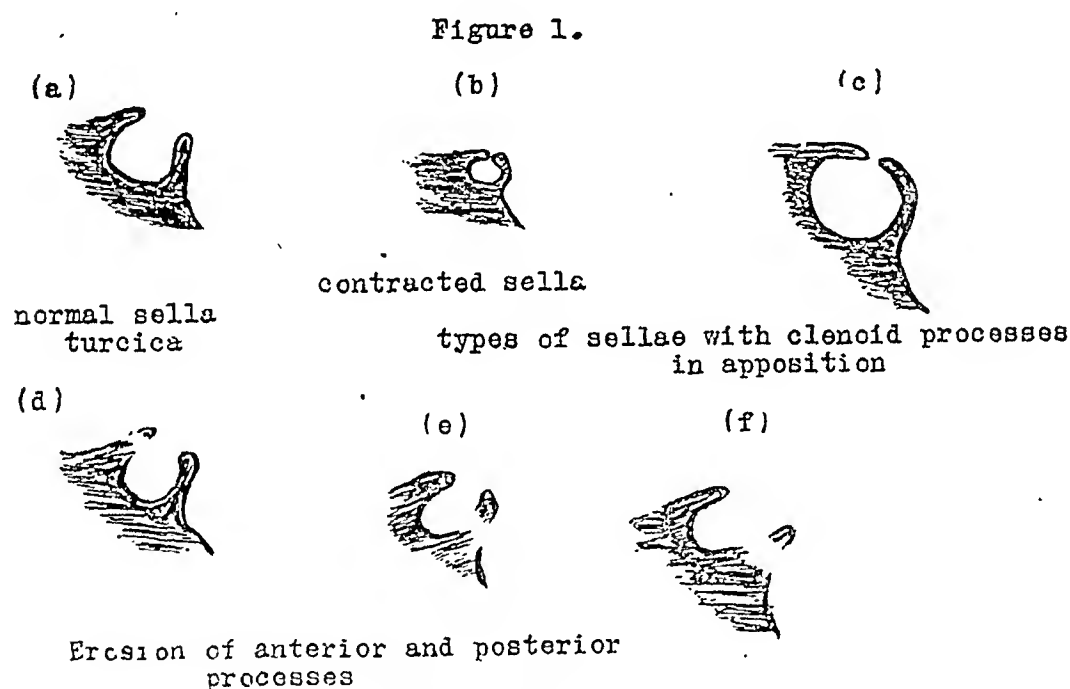


Fig. 1.—Various types of sella turcica.

latter hyperpituitary signs. Then again, there might be evidence of erosion of the posterior clinoid processes with, perhaps, pyramidal tract signs, or of the anterior processes with bitemporal hemianopsia or contraction of the visual fields, indicating in the former, enlargement of the gland posteriorly and in the latter anteriorly. There is also the generally enlarged sella turcica, the sella whose posterior process is tilted backward; and last of all, the complete destruction of the fossa and dorsum sellae, such as occurs in neoplastic overgrowth of that region. If a careful study of the physical signs and symptoms of the patient is made prior to the roentgen ray picture, the conformation of the fossa can frequently be prognosticated with considerable accuracy. Drawings of various types of sellae are shown in the accompanying diagram (Fig. 1).

Why the pituitary gland should enlarge is the next question that comes to mind. It is well known that during menstruation and pregnancy there is a physiologic enlargement of the gland, Falta noting an increase in weight from 0.6 to 1.0 gm. This enlargement may be cyclical and account for the periodical occurrence of the menses, or else we can ascribe it to stimulation from the gonadal secretion. Other glandular disturbances are also liable to influence the pituitary, etc., such as pineal or thymic subinvolution, adrenal or thyroid disease, which is most probably in the nature of a compensatory phenomenon.⁸ A mental shock or traumatism to the skull may be the exciting cause to an altered hypophyseal function. These occasionally result in a hyperplasia of the glandular elements, but the gland may be also the seat of colloid degeneration, cysts, abscess, hematoma, adenoma, adenocarcinoma, sarcoma, endothelioma and teratoma.

In many ways, therefore, we see there can occur a disproportion between the pituitary body and the sella with the production of pressure on the sensory nerves to the dura; and by its encroachment on the cavernous sinuses it may cause interference with the cerebral circulation, the whole setting up the train of pituitary symptoms, including the headache.

SYMPTOMS AND SIGNS

The pituitary headache has three characteristics: its location; its duration and persistence; and its relief under specific medication. A patient will come to the physician complaining of a frontal headache. On questioning further he will say that it is situated "deep in the forehead behind the eyes," often feeling as though it were pressing on them, giving a "dazed" sensation. Not infrequently, without asking, and always on asking, the patient, placing the finger on either temple, pointing directly inward at the hypophysis in the attitude of the accompanying picture will say, "Doctor, it is between here" (Fig. 2). Depending on its severity, it is described as a tightness between the temples, a feeling of pressure or distention, or an intense, bursting ache. Rarely they complain that there is a sensation of "something in there" and on moving the head, they may feel as though "a marble-like object were rolling about." Deep pressure on the temples may elicit some tenderness.

This headache is very persistent, usually lasting from one-half hour to forty-eight hours, and it may be continuous, frequently coming on in the female at the time of the menses. It often leaves very suddenly, returning again with exacerbations; it is accentuated by excitement, stooping over, and by the ingestion of sugar. At the climax of the headache we may see nausea and vomiting, with which there will come

8. Timme, W.: New York M. J., Oct. 16, 1915.

relief. Marked fatigue accompanies the headache, the patient hardly being able to drag himself about, and there is present to stroking a broad white skin line as evidence of suprarenal deficiency caused by the drain on the adrenal function by the exhausted pituitary. The patients feel slowed down in their activity, yawn excessively, are sluggish and willing at any moment to seek an opportunity for sleep. These patients are particularly prone to attacks of depression, which come on without any cause, and have as their basis some very insignificant fact. In children there is apt to be evidence of mental retardation, with dulness, sluggishness of the mind and lack of the higher reasoning powers, this usually occurring in hypopituitary conditions, while in adults we sometimes see a loss of moral control resulting in frequent visits to the police courts. The menstruation has certain characteristics in these pituitary individuals. It may begin very early, at the age of



Fig. 2.—Location of pituitary headache (Case 7). Note the coarseness of features and the nasal eyebrow.

10 or 12, or else very late, at 16 or 18. The periods are irregular, often coming every two or three weeks, and the flow excessive. Sexual development may be very precocious in the hyperpituitaries. Polyuria is occasionally present and constipation frequently accompanies the height of the headache with diarrhea at its termination.

Knowing that the pituitary, together with the adrenals, controls the mobilization of sugar in the body, it is not strange that these patients should have anomaly of sugar metabolism, as is seen in the periodic development of an intense craving for sweets, a sort of dipsomania, as it were, for sugar. The satisfaction of this desire being completed by eating candy, it is almost invariably followed by a typical pituitary headache. We can readily see that owing to the increased demand on it, there is an enlargement of the pituitary gland, and following on this the adrenals are called on to assist in mobilizing the sugar, the excessive drain on them causing great fatigue and the formation of a vicious circle.

How, then, are we to recognize these cases and tally their physical signs with the symptoms enumerated? Do we expect to see finished acromegals or giants, or adiposis with sex regression? No! but there are certain dyspituitary signs which are of aid in diagnosis.

The growth of hair has certain peculiarities; it is more apt to be dark and coarse in texture. The amount is abundant, the arms, legs and body being covered with a quantity of hair; the pubic hair not infrequently is of masculine type in the female, growing up to the umbilicus in a triangular fashion and in the male it may be of the female type, straight across over the mons veneris. The eyebrows are heavy and long and they often meet in the midline over the nose forming a nasal eyebrow. The female may show a tendency to a mustache. The bony framework is altered, there being either excessive length or breadth of bone, depending on whether or not the epiphysis had united when the metabolism was disturbed. The appearance of the face might show one or all of the following: eyes too close together or too far apart, a large nose, prominent superior maxillae, a prognathism of the lower jaw, a general coarseness of the features with thickening of the lips. The teeth, especially those of the upper jaw, either widely spaced or else unusually broad. These persons are sometimes very tall, with large hands and feet, and there is a broadening of the hands, with clubbed fingers. Deposition of adipose tissue may be excessive. Pulse and blood pressure are both apt to be low, especially during the headache, this being more an expression of adrenal exhaustion than pituitary. Blood sugar determination and sugar tolerance will in most of these cases reveal either too high or too low a figure. A contraction of the temporal fields of vision is occasionally found and, rarely, a primary optic atrophy.

TREATMENT

Specific remedies for the cure of disease constitute the treatment *par excellence* and modern medicine has given to us a number of such agents; for example, arsphenamin for syphilis, the employment of serums in pneumonia and epidemic meningitis, thyroid in myxedema and cretinism, etc. Such a specific is the administration of pituitary to cure pituitary headaches.

There are a number of good pituitary preparations on the market, the most satisfactory being Armour & Company's and Burroughs Wellcome's tablets of the whole gland. If the latter are used they should be prescribed in doses four times as large as any others. We commonly use Armour's tablets in doses varying from $\frac{1}{4}$ grain to 2 grains three times a day; an average for an adult is 1 grain, preferably given one hour after meals. Much larger doses are recommended by some authors, Cushing giving as much as 15 grains in some

of his cases. For a more rapid action it is claimed that hypodermic injection of pituitary extract, 0.5 to 1 c.c., is valuable, but I have seen better results with preparations of the whole gland.

Continuous medication with pituitary will result within a few days in a decrease in the intensity of the headaches; there will be a longer period between their occurrence, the head will feel less "tight," and fatigue, nausea, and vomiting will also disappear. An examination of the case reports given later will show very gratifying results. A number of these cases cure themselves, and it is the belief of Timme⁹ that the person who has a small sella turcica with dyspituitary signs and symptoms will remain so indefinitely, even though pituitary administration helps toward relief; but if the sella is large and there is room for expansion, there will occur the foregoing type of symptoms and the patients will eventually cure themselves, even though they become acromegalic in the process. We can therefore regard symptomless acromegalics as a finished product, according to this investigator.

But there are also those cases which, having symptoms of pituitary disease, do not improve on treatment, and it is then that we must begin to consider the possibility of a neoplasm and careful observation becomes essential. Just a word of caution against too long continued pituitary therapy. After the symptoms show improvement, diminish the dose and give it only three or five days out of the week; this gives the gland a chance to readjust itself.

Case reports follow, and as they are all from clinic patients, it has, unfortunately, been impossible to have blood sugar and sugar tolerance tests made.

CONCLUSIONS

1. Pituitary disturbances constitute a fairly common cause of headache.
2. Pituitary headache is located between the temples, deep in behind the eyes and is accompanied by dyspituitary signs.
3. Abnormality of the sella turcica is demonstrable in almost every case of pituitary disease.
4. Administration of the whole gland cures these headaches and the accompanying symptoms in a large percentage of cases, provided there is not a progressive neoplastic growth.

REPORT OF CASES

CASE 1.—J. T., a woman, aged 40, married, had severe frontal headaches beginning at the age of 15, with the onset of the menses. The headaches were infrequent, occurring usually once a month at the menstrual periods until six years prior to observation, since which time they have increased in severity and frequency so that they now come on several times a week. The head-

9. Timme: A New "Polyglandular Syndrome," "Endocrinology." 2:209, 1918.

ache lies between the temples and moving the head accentuates it. Vomiting has occurred about once in two weeks lately. The patient is fatigued at times and has polyuria, and the menses are always irregular. There has been no loss of appetite or craving for sweets. At the age of 30 she suddenly became very obese and increased in weight to 185 pounds. An aunt has goiter.

Physical examination shows a well developed woman, short, obese, with small hands and feet. The head is large, eyes set close together, jaw prognathous. The eyebrows are heavy, with nasal eyebrow marked. The teeth are small and not crowded, and fingers are broad, short and clubbed. The roentgen ray shows a general enlargement of the pituitary fossa, with slight erosion of the posterior clinoid processes (see Table 3, J. T.).

Pituitary, $\frac{1}{4}$ grain twice a day, was given. In one month the headaches and other symptoms had greatly improved. At the end of four months, during which time the dosage was increased to 1 grain daily, she said that she had only had two very slight headaches in the previous two months, and had had no nausea or vomiting for three months. Discontinuance of the drug caused a return of the old symptoms. This is evidently a case which originally began as hypopituitary and is now endeavoring to compensate and enlarge.

CASE 2.—D. S., aged 16, schoolboy, was brought to the hospital with a history of several blows on the head, complaining of momentary "staring" spells, followed by a very severe headache, with which he would go to bed. This headache is made worse by playing or excitement and is in the pituitary location. He has stood very low in school, is sleepy, dull and stupid. When younger he had enuresis and has always been fond of candy. Mental examination showed him to be a high grade imbecile, measuring 7 years on the Terman score, not being oriented as to time, and lacking in reasoning ability and judgment.

Physical examination showed a small boy who appears about 10 years of age; structural and sexual growth are backward, there being no secondary sex signs as yet. He has rather a square jaw, teeth are broad but not spaced, the eyebrows are normal in size and the hair growth is scanty. A roentgenogram of the skull shows a slightly enlarged sella turcica with heavy clinoid processes which completely roof over the fossa. (Table 3, D. S.)

On the evidence of the headaches, the roentgenogram, and a hyperpituitary type of father, the boy was given pituitary, $\frac{1}{2}$ grain three times a day. He returned in two weeks without headaches. At the end of a month the headache seemed gone for good, and there was as well a cessation of the "staring" spells. The father noted joyfully that he was less mischievous and more active. The dose was increased to 1 grain three times a day. After three months the boy says that he feels as though a "weight had been lifted off his mind," an observation he could not have made at the onset of his treatment. He is brighter, more interested, and is anxious to learn. He can tell date, year and season, and is standing much higher in his studies. Another mental test showed an advance of one year in three months' time. This is evidently a hypopituitary case which without treatment would never have come out of the imbecile class.

CASE 3.—E. W., woman, aged 24, single, came into the clinic suffering with severe frontal headache, slunk into a chair holding her head, yawned frequently, extremely fatigued, dull, drowsy, nauseated, trying to vomit. She had been this way for three days. As long as she can remember she has off and on had these terrible headaches. Since coming to America four years ago they have increased in frequency and severity; she is very irritable, is constipated, and has lost 42 pounds in weight. Her headaches are paroxysmal in type, lasting for a period of from a few hours to three days; are situated between the temples, and bore in like a knife, causing an aching of the eyes at times; and with the onset of vomiting they are often relieved. There has been no menstrual irregularity. The patient has at times an intense craving for candy. Her father's sister had similar headaches.

The patient is of medium height, large frame, skull is also large, eyes are far apart, jaw slightly prognathous, teeth broad and spaced, eyebrows heavy, with a marked nasal eyebrow; the feet are small. There is a slight but definite contraction of the temporal fields of vision. The fundi show the veins engorged. The roentgenogram shows a rather large sella with clinoid processes in apposition and beginning erosion anteriorly. (Table 3, E. W.)

Pituitary, 1 grain three times a day, was given; increased after three weeks to 2 grains three times a day. In a week there was an improvement in the intensity of the symptoms and in a month the headache had diminished so that the patient has only had a slight ache once in two weeks. There has been no nausea or vomiting, fatigue is very much less, and she is anxious to return to work. She seems much brighter and more active mentally; there is less visual field contraction, and she has gained 5 pounds in weight. Improvement is continuing.

CASE 4.—N. C., a nurse, aged 29, single, when a little girl had headaches all the time, which were made light of by her family because of her robust physique. She was given glasses, which have been frequently renewed, all with no relief. Headaches are severe, coming on in exacerbations in the "pituitary" location, bursting in type and accompanied until one year prior to observation by nausea and vomiting and confining her to bed. Although a large, strongly built woman, she is always fatigued and sleepy and when the headache is most intense she is dull, drowsy and wants to sleep. Several years ago she noticed that on satisfying her craving for sugar the headache became worse, so she does not eat it now. She is constipated at times and has polyuria; also has mild periods of depression. The menses began at 12 years and have been irregular ever since.

The patient has always been big, coming from a tall family. The hands and feet are large and the maxillae are prominent. The eyebrows are bushy and continuous across the nose. The hair growth is plentiful and there is a slight tendency to the masculine pubic hair. The roentgenogram shows a generally enlarged sella turcica, wide open and very deep. (Table 3, N. C.)

Pituitary, 1 grain twice a day, was given, followed by a cessation of the headaches and a diminution of the fatigue within twenty-four hours. The patient since has had only one slight recurrence of the headache, and fatigue and dulness are much improved.

CASE 5.—N. F., a nurse, aged 27, single, had her first headache at 16, which was very severe, and at intervals ever since they have recurred. Coal tar drugs were often taken, with only slight relief. The menses began at 14, then skipped six months, and became regularly established at 16, since when they have been irregular. The headache usually comes a week before the catamenia and continues until the onset; then relief comes. It is typically pituitary in location, between the temples and on top of the head, described as a feeling of tightness, pressure and distention, accompanied by fatigue and occasionally depression. The patient faints easily, has excessive perspiration of the hands and cyanosis of the extremities, and has also a desire for sweets, satisfaction of which causes headache.

The patient is small, thin, square built; skull round, jaw broad, prognathous; hands and feet small, short, stubby; eyebrows heavy, with marked nasal eyebrow; tendency to moustache. Hair growth is excessive on hands and legs; pubic hair masculine in type. A roentgenogram shows that the sella is enlarged anteroposteriorly and there is slight erosion of the posterior clinoid process. (Table 3, N. F.)

Pituitary, $\frac{1}{2}$ grain three times a day. In three days the patient noticed that the head did not feel quite so "tight" between the temples. The next period was preceded by a headache, which was not so severe, and the second was accompanied by only a slight dazed feeling. The headache is now gone.

CASE 6.—M. B., a cook, aged 31, married, five years prior to observation had very severe headaches previous to the birth of her first child; since then

she has suffered with them off and on, becoming worse during the previous six months, lasting a whole day, forcing her to bed, and obtaining relief only by vomiting. She had glasses fitted and teeth extracted without relief. The headaches are described as severe, situated between the temples, behind the eyes, accompanied by fatigue, dizziness and sleepiness. She feels "dopy," sluggish and has no ambition, becomes depressed and unhappy and does not wish to be bothered. The menstruation began at 14 and comes every three weeks. She has no desire for sweets.

The patient is a large, obese woman, weighing 164 pounds, with scanty growth of hair. The teeth are broad, eyebrows heavy, with only a few hairs over the nose; the jaw is broad and slightly prognathous. This woman is hypopituitary in most features and the roentgenogram was no surprise when it revealed an extremely small, contracted sella turcica, with heavy clinoid processes meeting in the midline. (Table 3, M. B.)

This patient has been under treatment only a few months, but in that time has had no suspicion of a headache and says voluntarily that she feels less tired and dopy and is brighter and more ambitious. Medication has been 3 grains daily of the whole gland.

CASE 7.—W. G., a sailorboy, aged 23, single, has had severe frontal headache for five years. The tonsils were removed and glasses procured without relief. The headache is boring, bursting in type, deep in the midline between the temples, as in his picture (Fig. 2). It is accompanied by extreme fatigue and at times the patient has a craving for candy. He is depressed frequently, feels mentally sluggish, his grasp is slow and his memory not so acute as formerly. He says that his hands and feet are larger and his face broader.

The patient is of medium height, has coarse, heavy eyebrows, with nasal accentuation, his nose and lips are large, features coarse, jaw prognathous, lower teeth spaced, the upper broad, hair growth is abundant, masculine type, and the hands and feet are large and square. The roentgenogram shows a small, flat sella with beginning erosion of the anterior clinoid processes. This is a hyperpituitary case which approaches more the acromegalic than any of the others.

Pituitary, 1 grain three times a day, was given. In one week the head felt clearer than in a number of years and the ache was less marked. The patient now has only a very slight headache at times, but notices particularly that his mind is more active, more attentive, and that he has a better grasp.

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A STUDY ON THE ETIOLOGY OF CHOLECYSTITIS AND ITS PRODUCTION BY THE INJECTION OF STREPTOCOCCI *

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In 1914, Rosenow,¹ by making cultures from the emulsified wall of the gallbladder of selected patients, found streptococci in most instances, and reproduced cholecystitis in animals by injecting intravenously the freshly isolated organisms. The work recorded in this report is similar to that of Rosenow, except that all gallbladders removed in operations in the Mayo Clinic, regardless of the degree of pathologic changes, were cultured.

The tissues were cultured as soon as possible after their removal, every effort being made to prevent contamination. Immediately before emulsifying, the tissues were thoroughly washed in large volumes of physiologic sodium chlorid solution. They were then ground in mortars within sterile air chambers or in a hood, the air of which was washed by means of steam from a sterilizer fastened to the end of the hood. The operator wore gloves and sleeves which, with the materials used, were sterilized in the sterilizers opening into the hood.

The emulsions thus made were inoculated in varying concentrations into tall columns of dextrose brain broth, blood broth, litmus milk, ascites dextrose broth, ascites dextrose agar and dextrose agar. Krumwiede plates of dextrose blood agar and plain blood agar plates were poured also. The cultures were studied at the end of twenty-four hours, but those that were negative were examined daily for a week.

Altogether, cultures were made from seventy gallbladders and four ulcers. At first cultures were also made from the contents of the gallbladders, but because of the large number of negative results, regardless of the findings in tissues, this was abandoned.

The duration of the symptoms in the cases studied ranged from three months to thirty years. The pathologic changes ranged from slight to marked thickening of the walls. The results of the cultures are summarized in Table 1.

* From the Division of Experimental Bacteriology, Mayo Foundation.

1. Rosenow, E. C.: The Newer Bacteriology as Determined by Special Methods, J. A. M. A. 58:903, 1914; *ibid.*, Etiology of Cholecystitis and Gallstones and Their Production by the Intravenous Injection of Bacteria. J. Infect. Dis. 19:527, 1916.

In the gallbladders showing slight changes 30 per cent. only yielded streptococci, in contrast to 75 per cent. in those showing marked changes. Moreover, the gallbladders in which marked changes existed showed the larger number of colonies. Some of these contained countless numbers of organisms, while those showing slight changes, with few exceptions, contained a small number. Of the latter, 58 per cent. gave no growth, while only 25 per cent. of those showing marked changes gave no growth. In the cases showing slight changes, colon bacilli were isolated in pure culture from 12 per cent. and in combination with streptococci from 6 per cent. The entire 15 per cent. of those with marked changes contained both colon bacilli and streptococci.

Some of the organisms, when first isolated, produced opaque, indifferent colonies on blood agar, and microscopically were grouped in diplococcus-forms with little or no chain formation. Further study, however, proved them to be streptococci. In this connection an interesting observation was made. From one of these cases, showing a pure culture of opaque gray staphylococcus-like colonies, two strains derived from a single colony were studied. The one kept on blood agar alternately aerobically and anaerobically became a green-producing streptococcus. The other, planted alternately in dextrose brain broth and on aerobic and anaerobic blood agar slants, developed hemolytic powers.

TABLE 1.—RESULTS OF CULTURES

Material Cultured	Number	Per Cent. Showing		
		Streptococci	Colon Bacilli	No Growth
Gallbladders showing slight changes.....	50	30	18	58
Gallbladders showing marked changes...	20	75	15	25
Ulcers	4	100	0	0

The different strains varied somewhat in their fermentative powers. Of the eighteen studied, all fermented dextrose, lactose and maltose, three raffinose, four mannite, ten salicin and one inulin. One strain, after a single animal passage, had its fermentative powers changed, but it was still agglutinated, the same as the original strain.

Microscopic examination of the gallbladders failed to reveal bacteria when negative cultures were obtained, but bacteria were found consistently when the cultures were positive. Organisms were found in the lesions produced in rabbits, but were not found in normal tissue. At the suggestion of Dr. E. S. Judd, microscopic examination of liver sections which he removed were made in ten cases. Interlobular cirrhosis was found in six, no change in two, and a bile-duct involvement

in two. The livers which were normal and those showing fibrotic changes were found in cases in which the gallbladders showed marked and slight changes, while in those showing cholangitis there was little or no change.

ILLUSTRATIVE CASES AND ANIMAL EXPERIMENTS

CASE 55.—A man aged 34 years, for the past two years had had gastric symptoms. Pains were aggravated by food, and soda gave no relief. He was operated on Aug. 20, 1918. The stomach was normal, the gallbladder showed slight changes and contained one large stone, the appendix showed slight changes; these two organs were removed. About 3 c.cm. of the fundus of the gallbladder was cultured.

August 21, all the cultures showed indifferent streptococci in pure form. Five c.c. of the dextrose brain broth culture was injected intravenously into Rabbit 1662.

August 22, the rabbit appeared to be well.

August 23, the rabbit appeared to be well; it was chloroformed, and the gallbladder was found greatly distended with watery bile; the walls were edematous. The stomach, spleen, kidneys, appendix, lungs and heart were normal. No other lesions could be found.

August 24, cultures made from the blood of the rabbit were negative, while those from the bile and gallbladder showed countless numbers of the injected streptococcus.

August 26, cultures were made from the pus expressed from the patient's tonsils.

August 27, the blood agar plate cultures showed indifferent and green-producing streptococci and colon bacilli. The dextrose brain broth cultures from the tonsil, containing both streptococci and colon bacilli, were injected intravenously into Rabbits 1682 and 1683.

August 28, both animals were found dead. Necropsy showed marked post-mortem changes but no evidence of specific localization. Five c.c. of the dextrose brain broth culture made from one of the indifferent colonies of streptococci was injected intravenously into Rabbit 1686.

August 29, the rabbit seemed well.

August 30, the rabbit seemed well; it was chloroformed, and the gallbladder was found edematous and distended. There were several small hemorrhages and white necrotic areas in the fundus. No other lesions were found.

August 31, cultures from the blood were negative. Cultures from the gallbladder showed streptococci in pure form. Microscopic examination of the gallbladder revealed streptococci in the tissues.

The primary cultures from three other cases of cholecystitis were injected intravenously in rabbits. The gallbladders in two of these showed marked changes and cholecystitis developed in each of the two rabbits injected. The streptococcus was recovered from the gallbladders in each, while the blood was sterile. The third strain isolated from a gallbladder having chronic changes showed no definite localization.

CASE 58.—A man, 68 years of age, had had intermittent attacks of pain in the region of his stomach for the past thirty years. The pain was worse in the afternoon and was not affected by food. He was operated on Aug. 21, 1918. An ulcer, 1.5 cm. in diameter and 4 mm. deep, with markedly indurated walls, was found on the lesser curvature of the stomach about 5 inches from the pylorus. The ulcer was excised.

August 22, cultures of the emulsified ulcer showed streptococci in pure form. Five and 8 c.c. of the dextrose brain broth culture from the ulcer were injected intravenously into Rabbits 1675 and 1676, respectively.

August 23, Rabbit 1675 seemed well. Rabbit 1676 was found dead. The cardiac end of the stomach showed fourteen punctate hemorrhages with sur-

face erosion. There were no other lesions except coccidial abscesses in the liver and in the inguinal region.

August 24, cultures from the blood and bile were negative. Cultures from the lesions in the stomach gave streptococci in pure form. Rabbit 1675 seemed well. It was chloroformed, and the cardiac end of the stomach showed several punctate hemorrhages with beginning ulceration. Other lesions were absent.

August 25, cultures from the blood and bile gave no growth. Cultures from the affected areas of the stomach gave streptococci in pure form.

August 26, cultures were made from the pus expressed from the patient's tonsils.

August 27, the blood agar plate cultures contained colon bacilli and green-producing streptococci. Three c.c. of the dextrose brain broth culture containing colon bacilli and streptococci from the tonsils were injected intravenously into Rabbit 1681.

TABLE 2.—RESULTS OF AGGLUTINATION EXPERIMENT

Serums	Dilutions of Serums	Tonsil	Gallbladder	Ulcer	Ulcer	Ulcer
		Case 55	Case 55 After One Animal Passage	Case 58	Case 58 After One Animal Passage	Case 75
Case 55 (Cholecystitis)	1-2	0 cloudy	++	+	0	0
	1-4	++	++	+	0	0
	1-8	++	++	+	0	0
	1-20	0	++	0	0	0
	1-100	0	—	0	0	0
	1-500	0	0	0	0	0
Case 58 (Ulcer of Stomach)	1-2	0	++	+	++	0
	1-4	0	0	++	+++	++
	1-8	0	0	++	++	++
	1-20	0	0	++	+	0
	1-100	0	0	+	0	0
	1-500	0	0	+	0	0
Normal Control	1-2	0	0	+	++	0
	1-4	0	0	+	+	0
	1-8	0	0	+	0	0
	1-20	0	0	0	0	0
	1-100	0	0	0	0	0
	1-500	0	0	0	0	0
NaCl Control	1-1	0	0	0	0	0

August 28, the animal was found dead. There were marked postmortem changes, but no evidence of localization.

August 29, cultures from the bile were negative. Cultures from the blood showed countless numbers of green-producing streptococci.

One other rabbit was injected with streptococci from an ulcer. It showed definite lesions in the stomach as did the others. Cultures made from the lesions showed streptococci, while those from a normal portion of the stomach were negative.

To determine further the specificity of the organisms isolated, serums were obtained from the cases cited for agglutination purposes.

As shown in Table 2, the serum of the patient with cholecystitis agglutinated both the strains from the tonsil as isolated, and the strain from the gallbladder after one animal passage, but failed to agglutinate the ulcer strains. The serum of the patient with ulcer, on the other hand, agglutinated the homologous ulcer strain as isolated, and after one animal passage, and the strain from another case of ulcer, but not the cholecystitis strains. The normal human serum had little or no agglutinating power over any of the strains.

SUMMARY

By making cultures of the emulsified tissues of gallbladders or adjacent lymph glands, streptococci are found to be the chief microorganisms associated with cholecystitis. The direct etiologic relationship of the streptococcus is established by their presence, often in numbers proportionate to the degree of gross and microscopic changes, by their having elective affinity for the gallbladder of animals and by the specific agglutinating power of the serum of the patient from whom isolated. The elective affinity for the gallbladder of animals of the strains from the tonsils indicates strongly that cholecystitis is commonly a blood borne infection from a focal source.

THE PHYSIOLOGIC ACTION OF CANTHARIS*

S. MORGULIS, M.D., AND A. L. MUIRHEAD, M.D.

OMAHA

The article by S. T. Lipsitz¹ and collaborators on polycythemia induced by cantharis attracted our attention, inasmuch as it bore on a problem under consideration in this laboratory. Since the physiologic action of cantharides tincture has not been made clear by the work just referred to, and we could find nothing in the literature to elucidate this matter, we decided to perform experiments with this substance.

Lipsitz discovered in a case of acute cantharis poisoning which came under his observation a marked polycythemic condition. He and his collaborators have extended their investigation of this interesting phenomenon to animals. In this way they corroborated the observation that the administration of cantharis induces a lasting polycythemia. The question of the causation of this polycythemia, however, received no answer from their study. Several possibilities may be considered in this connection. The polycythemia may have resulted from vasomotor changes whereby an extra amount of erythrocytes from the deep organs is forced into the peripheral circulation. Thus, the appearance of polycythemia may be produced. That such an increase in the number of red cells through a redistribution of the formed elements of the blood sometimes occurs has actually been observed. Could the cantharis effect, which may last for days, also be due to a vasomotor reflex? The long persistence of the effect would probably be against this suggestion, but as we could find no information as to the influence of cantharis on blood pressure, we undertook several experiments with this in view.

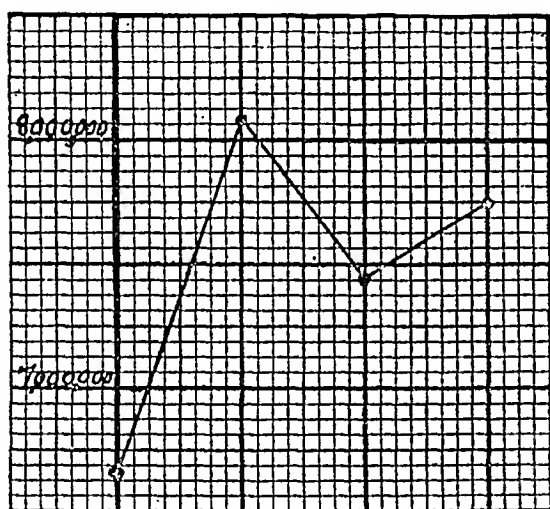
A female dog weighing 9 kg. was used. The animal received 2 grains of morphin subcutaneously; then it was put under ether anesthesia, which was continued throughout the experiment. The blood pressure was recorded from the carotid artery. Five drops of cantharides tincture in Ringer's solution was injected into the external jugular vein. There was no effect on the blood pressure, but the respiration became more frequent. After five minutes another five drops of the tincture in Ringer's solution was injected, and five minutes

*From the physiological laboratory of the Creighton University College of Medicine.

1. Lipsitz, S. T., Fuerth, A. L., and Cross, A. J.: Polycythemia Induced by Tincture of Cantharides, *Archives Int. Med.* 20:913, 1917.

later this was again repeated. No change in the blood pressure was obtained.

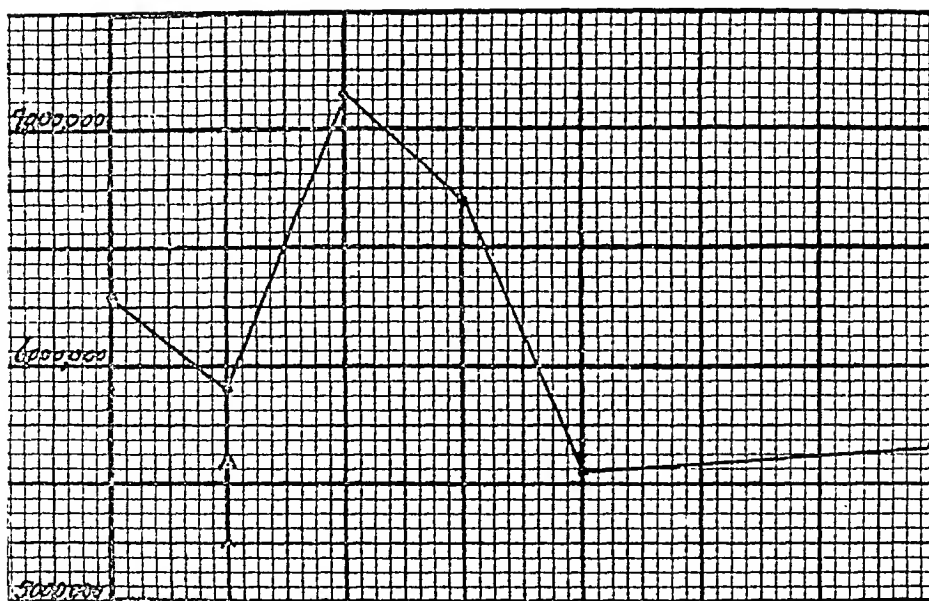
In another experiment with a male bulldog weighing 20 kg. we injected intravenously the equivalent of about 1 mg. of cantharidin per kilogram of body weight. (Computed from the fact that the tincture is 10 per cent. strong, and that the cantharis powder contains approximately 0.5 per cent. of the active principle.) The dog was etherized, and the carotid blood pressure as well as the respirations were graphically recorded. After a normal tracing had been obtained for several minutes, 40 c.c. of the tincture, made up to 100 c.c. with Ringer's solution, was injected into the femoral vein. The injection was made slowly, at the rate of 5 c.c. per minute. A very slight rise in pressure was observed at first. The respiration was very rapid and



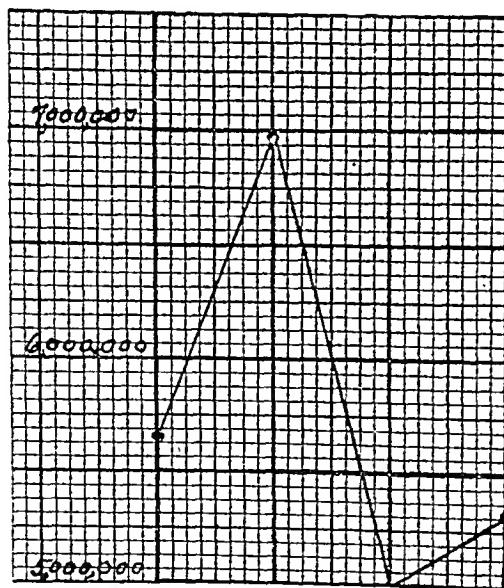
Experiment 1.—White rabbit; weight 7 pounds; normal; erythrocytes, 6,640,000; 25 drops of cantharides tincture were given by stomach tube: First day, erythrocytes, 8,072,000; second day, 7,440,000; third day, 7,766,000.

labored, and synchronous with the pulse. A distinct rattling sound in the chest could be heard. Twenty-five minutes after the injection the blood pressure remained practically normal.

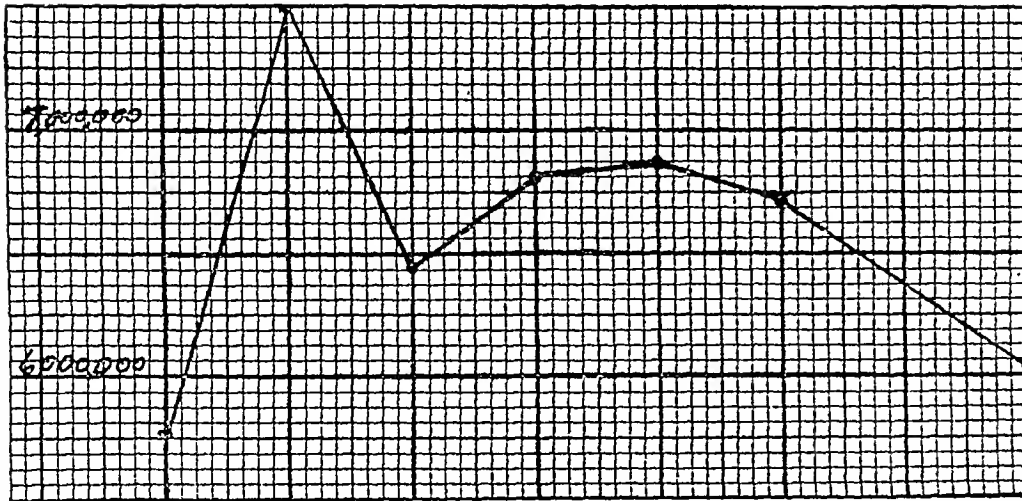
In a third experiment we used a male dog weighing 12.5 kg. The ether anesthesia was preceded by morphin. The blood pressure was recorded from the carotid. The cantharides tincture was injected into the external jugular. Twenty-five c.c. were injected at first, and fifteen minutes later this was followed by a similar dose. In other words, the equivalent of about 2 mg. of cantharidin per kilogram was injected into the blood. The carotid pressure remained normal for over an hour. Later it rose slightly above the original level. One hour and forty minutes after the injection the dog suddenly died.



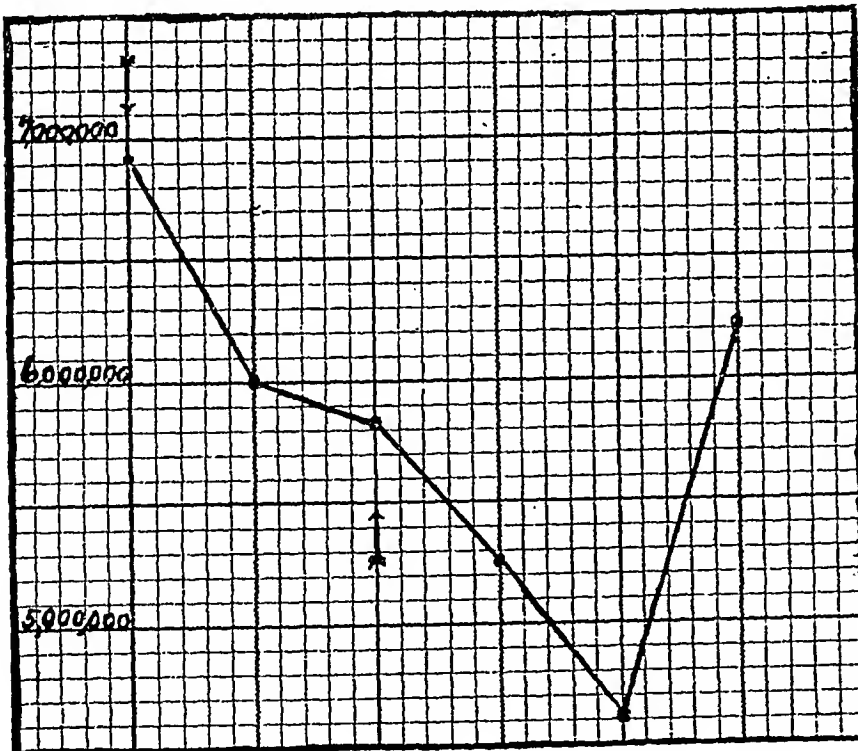
Experiment 2.—Black rabbit; weight, 5 pounds; normal; erythrocytes, 6,292,000; normal; erythrocytes, 5,906,000; 20 drops of cantharides tincture in 0.9 per cent. sodium chlorid solution injected into the vein of the ear: First day, erythrocytes, 7,140,000; second day, 6,692,000; third day, 5,542,000; sixth day, 5,650,000.



Experiment 3.—Black rabbit; normal; erythrocytes, 5,650,000; 1 c.c. of cantharides tincture in 0.9 per cent. sodium chlorid solution injected into vein of the ear: First day, erythrocytes, 6,975,000; second day, 4,963,000; third day, 5,313,000.



Experiment 4.—Black rabbit; weight, $4\frac{1}{2}$ pounds; normal; erythrocytes, 5,763,000; 2 c.c. of cantharides tincture given by stomach tube: First day, erythrocytes, 7,500,000; second day, 6,450,000; third day, 6,812,000; fourth day, 6,875,000; fifth day, 6,713,000; seventh day, 6,038,000.



Experiment 5.—Same rabbit; normal; erythrocytes, 6,917,000; 1 c.c. of cantharides tincture injected into vein of the ear: First day, erythrocytes, 6,001,000; second day, 5,830,000; 2 c.c. of cantharides tincture given by stomach tube: third day, erythrocytes, 5,270,000; fourth day, 4,610,000; fifth day, 6,220,000.

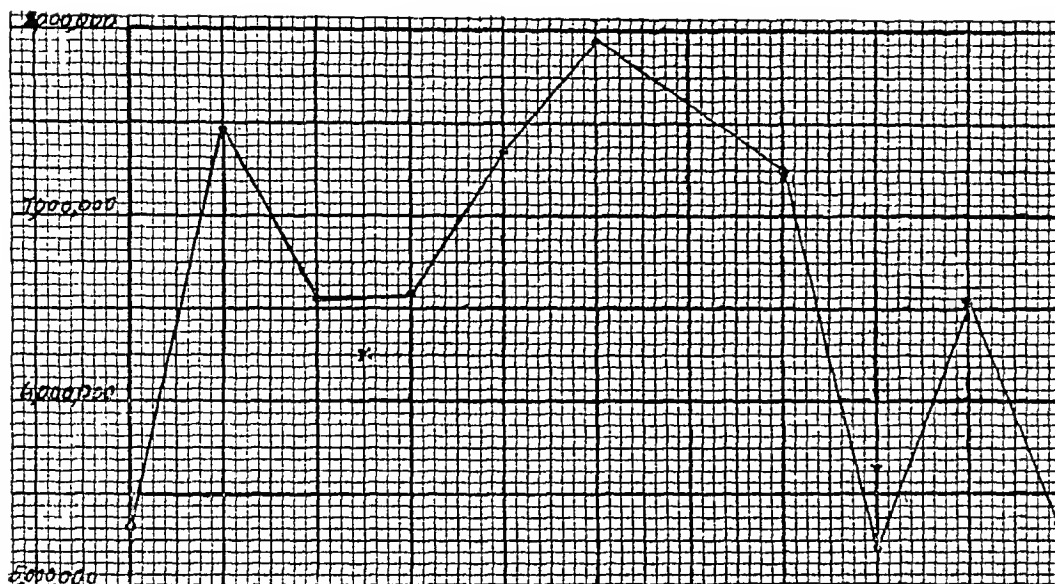
The necropsy findings were rather suggestive. The intestine, pancreas and spleen were grayish purple; the liver very dark and congested; the kidneys firm and strongly congested. The heart was in diastole; the veins were greatly distended with blood. The lungs were overfilled with blood, very hard and covered with dark purple patches.

Having thus failed to find any influence on the general blood pressure which might perhaps have explained the origin of the cantharis polycythemia, we turned our attention to another possibility, namely, the stimulation of the red cell-producing organs. We examined for this purpose specimens of blood from rabbits both before and after treating them with cantharides tincture. The blood was obtained by pricking the vessels of the ear. Smear preparations were made and the red and white count determined each time. To make the results strictly comparable, the same degree of dilution was always used.

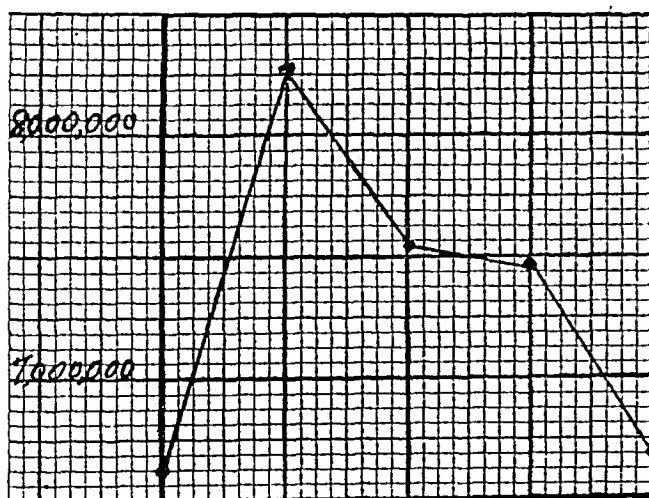
The stained preparations were carefully searched for evidence of new cell formation, and although dozens of slides were examined, we never found any normoblasts. In general, it may be said that the blood picture with the differential stain remained unchanged.

The leukocyte count proved of little or no consequence, but the enumeration of erythrocytes in our experiments with rabbits threw much light on the problem. In the following experiments the tincture of cantharides was administered to rabbits either by stomach tube or intravenously. The effect of these two modes of treatment was quite different, and this difference we think is significant in the interpretation of the cantharis "polycythemia." Before we record our experiments, however, we wish to point out that in our experience the cantharis is not nearly as toxic as it appears from Lipsitz' investigation. Our tincture was prepared from the best article on the market (Russian powdered cantharis) according to the United States pharmacopeia.

An examination of the data and curves just presented corroborate Lipsitz' observation of a lasting increase in the red cell count following the administration of cantharides tincture by stomach. It should be noted, however, that according to our experience the results following the administration of cantharis intravenously differ fundamentally from those occasioned by cantharis given by stomach. A glance at the curves shows this at once. Instead of a polycythemia lasting several days, the increase in the red cell count induced by an intravenous injection of cantharis is followed within forty-eight hours by a drop to the normal level or even below that. This striking difference in the durability of the effect on the blood is evidently associated with the rapidity of the elimination of the cantharis. Given by stomach it evidently acts as a gastro-intestinal irritant, being slowly absorbed and gradually eliminated through the kidneys. Introduced into the blood



Experiment 6.—Black rabbit; weight, $5\frac{3}{4}$ pounds; normal; erythrocytes, 5,315,000; 2 c.c. of cantharides tincture given by stomach tube: First day, erythrocytes, 7,470,000; second day, 6,550,000 (gave birth to two young); third day, 6,580,000; fourth day, 7,350,000; fifth day, 7,960,000; seventh day, 7,250,000; eighth day, 5,190,000 (1 c.c. injected into the vein of the ear); ninth day, erythrocytes, 6,540,000; tenth day, 5,350,000.



Experiment 7.—White rabbit; weight, $4\frac{1}{2}$ pounds; normal; erythrocytes, 6,630,000; 2 c.c. of cantharides tincture given by stomach tube: First day, erythrocytes, 8,270,000; second day, 7,540,000; third day, 7,470,000; fourth day, 6,680,000.

the cantharis reaches the kidney by a more direct route, and is more quickly discarded. In both events, apparently, its elimination is associated with a loss of water, resulting in a concentration of the blood. The would-be polycythemia is therefore nothing but a state of blood concentration.

Experiment 5 suggests that rabbits may develop a certain immunity toward cantharis. This rabbit received cantharis four times, both intravenously and by stomach. When the tincture was given again intravenously a marked diminution in the erythrocyte number took place. The tincture was then given by stomach tube, but the red cell count continued to fall off. Thus from 6,917,000 per square millimeter the number diminished to 4,610,000 in five days. It then returned to the normal level again (6,220,000).

From our investigation we can conclude that in cantharis we do not possess a means of experimentally inducing polycythemia, inasmuch as it does not cause a production of new red cells, but merely occasions a condensation of the blood through the loss of water in the process of elimination of cantharis by the kidneys.

HYDROCEPHALUS AND CHOKED DISK IN DOGS *

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It can not be said that consideration of the subject of choked disk is a new thing, but, as long as the correct explanation of the origin of choked disk alone can give a satisfactory conception of its clinical significance, any additional data based on experimental observations may help to decide a question which already has called forth numerous discussions and an abundance of conflicting theories.

These discussions began with von Graefe, and since the appearance of his original article on this subject two principal theories have claimed most attention. According to one, choked disk finds its origin in local inflammatory reactions, while the other explains its occurrence on the basis of purely mechanical factors.

Historically, the mechanical theory is the oldest and was first advanced by von Graefe.¹ He believed that the increased intracranial pressure, acting by compression on the cavernous sinus, caused a stasis in the ophthalmic vein, which resulted in a choked disk. But, several years later, von Graefe saw the fallacy of this view when Seseman demonstrated the free anastomosis between the ophthalmic and facial veins. Therefore, the inability of the ophthalmic to empty into the cavernous sinus could no longer be considered as a cause.

The exceedingly rare occurrence of choked disk in cases of cavernous sinus thrombosis, as has been pointed out by Uhthoff,² and the experimental demonstration that even extreme direct compression of the sinus is insufficient to induce the appearance of a swollen disk, is additional proof that its pathogenesis does not lie in a failure of the retinal and optic veins to empty into the cavernous sinus.

Such factors as these led Schmidt-Rimpler,³ after Schwalbe⁴ had shown that the intravaginal lymph spaces of the optic nerve communicate with the subarachnoid space of the brain, to suggest a direct driving of cerebrospinal fluid through the lamina cribrosa with an edematous infiltration of the nerve head as a consequence.

* Contribution 65 from the Departments of Anatomy and Pharmacology, Northwestern University Medical School, Chicago.

1. Von Graefe: *Arch. f. Ophthal.* **7**:56, 1860.

2. Uhthoff: *Neurol. Centralbl.* **23**:903, 1904.

3. Schmidt-Rimpler: *Arch. f. Ophthal.* **15**:193, 1869.

4. Schwalbe: *Arch. mikr. Anat.* **6**:1, 1869.

This meant that a hydrops of the nerve sheath existed, and Manz⁵ argued that since this sheath was under tension, it caused compression of the optic nerve vessels as they pass through the lamina cribrosa and that this would result in an edema of the disk.

This view, which regards the rise in intracranial pressure as the primary factor, and possibly acting through compression on the vessels as they pass through the lamina cribrosa or nerve, has found adherents in Cushing and Bordley,⁶ and is by many considered as the most satisfactory explanation offered so far.

The number of those who regard choked disk as a manifestation of an inflammatory process has steadily decreased. Toxic substances, the product of tumor cells or of inflammatory processes in the meninges, were thought to be carried by the blood or lymph stream to the optic disk and there caused a local reaction which made itself apparent in a swollen disk. With slight variations these views found adherents in Gowers,⁷ Leber,⁸ Deutschman,⁹ Elschning,¹⁰ Lawford and Edmunds¹¹ and others.

But, within the last few years the inflammatory theory has been accepted by few as a satisfactory explanation. This is especially true since Paton and Holmes¹² have published their histologic studies of postmortem findings in several hundred cases of choked disk occurring in association with cerebral tumors. They report that in the early stages a simple edema without round cells is the prominent feature. Even in cases of long standing the characteristics present are not those of an inflammatory process. If any inflammation exists the picture is such that it must be considered as merely secondary to the disturbance produced by the edema.

These findings of Paton and Holmes on such abundant clinical material have been corroborated by similar pictures in experimental animals. They may, therefore, be considered as quite conclusive evidence against the theory that choked disk, in tumor cases at least, is due to an inflammatory reaction; whereas the importance of increased intracranial pressure stands out prominently. The full meaning of this was recognized by Parsons,¹³ who says: "All those who have had opportunity to watch the extraordinary effect of the relief of intra-

5. Manz: *Deutsch. Arch. f. klin. Med.* 9:339, 1872.

6. Cushing and Bordley: *J. A. M. A.* 52:353, 1909.

7. Gowers: *Medical Ophthalmoscopy*. London, 1879.

8. Leber: *Tr. First Internat. Cong.*, London 3:138, 1881.

9. Deutschman: *Neurol. Centralbl.* 23:673, 1904.

10. Elschning: *Arch. f. Ophthal.* 41:179, 1895.

11. Lawford and Edmunds: *Tr. Ophthal. Soc.* 3:138, 1883.

12. Paton and Holmes: *Brain* 33:389.

13. Parsons, J. H.: *The Pathology of the Eye*, 2:1350, 1908.

cranial pressure on a choked disk must agree that no theory which leaves this element out of account requires further consideration."

Numerous attempts have been made to sift the conflicting facts and theories of the origin of choked disk by experimental studies. A sudden increase of intracranial tension was always an essential feature in the methods employed.

Manz,¹⁴ one of the first of the experimental workers on this subject, noted that fluids injected into the subdural space passed into the nerve sheath. An engorgement of the retinal veins and a transient swelling of the optic disk resulted from this.

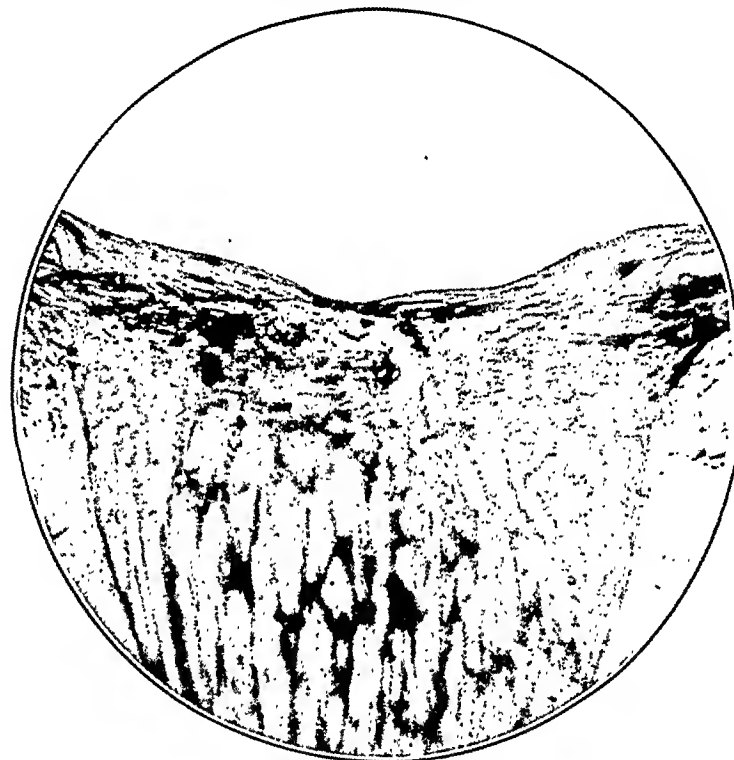


Fig. 1.—Photomicrograph of disk and optic nerve of a dog. Normal.

While Manz was unable to demonstrate a permanent choked disk by this same method, Schieck¹⁵ succeeded and produced a definite optic disk swelling. However, when he placed sponge tents under the skull or created artificial tumors through the subdural injection of paraffin, he failed. From this he concluded that a mere rise in intracranial pressure is insufficient and that an increased amount of cerebrospinal fluid is an essential.

Levinsohn¹⁶ observed a venous hyperemia and some retinal hemorrhages after injecting fluid, but did not find any evidence that the high tensioned cerebrospinal fluid permeated through to the vaginal sheath spaces.

14. Manz: München. med. Wchnschr. 35:531, 1888.

15. Schieck: Die Genese der Stauungspapille, Weisbaden, 1910.

16. Levinsohn: Ber. d. Ophth. Gesellsch., Heidelberg, 1911.

With fluid injected under considerable pressure into the subdural space, Cushing and Bordley¹⁷ produced an acute edematous swelling of the nerve head and retina. Digital pressure when exerted for a period of several minutes against the dura and also elastic foreign bodies when placed between the skull and dura caused a like optic picture.

Parker,¹⁸ within the last years, published findings based on a difference in tension in the two eyes and a subsequent creation of intracranial pressure produced by the usual methods; but the most satisfactory results were obtained by the use of sponge tents. His experi-



Fig. 2.—Section of choked disk, right eye, Dog 2.

ments were carried out on dogs and monkeys with identical results. He found that the eye that possessed the least tension is the first to show choked disk.

It is evident from the foregoing summary of these experimental methods that they have in the main caused a sudden increase in cerebral pressure. This created conditions which resembled such as are present in sudden hemorrhages and edema of the brain and in no ways are comparable to the gradual process which accompanies the growth of cerebral tumors or development of hydrocephalus. Any new experimental work, therefore, which attempts to explain the cause of choked disk should create conditions that will cause the same gradual changes

17. Cushing and Bordley: *Bull. Johns Hopkins Hosp.* 20:95, 1909.

18. Parker: *J. A. M. A.* 17:1052, 1916.

that occur and are observed clinically. In the hope that this could be attained with the following method and that new information might result the present work was undertaken.

EXPERIMENTAL METHODS AND OBSERVATIONS

Because of the difference in the optic blood supply between canines and primates, the results obtained through experimentation on dogs by other workers on this subject have frequently been held as being nonapplicable to man. On account of this criticism it was decided to create a condition the existence of which in man, namely, hydrocephalus, is known to be accompanied almost always by choked disk.



Fig. 3.—Section of choked disk, left eye, Dog 2.

To induce the formation of hydrocephalus the aqueduct of Sylvius was blocked with soft paraffin. The paraffin had a melting point ranging around 42 C., and was only used at a temperature just sufficient to prevent hardening while in the equally warmed syringe.

After several experimental attempts it was found that a small trephine opening, when placed 6 mm. above the highest nuchal line and 5 mm. to the right or left of a line carried forward from the center of the external occipital protuberance, would permit a needle to pass just in front of the tentorium cerebelli. By this route it is possible to be guided by the bony tentorium and damage to the longitudinal sinus is easily avoided. Since the lower edge of the tentorium practically touches the upper surface of the pons, it is necessary to

depress the needle only 1.5 or 2 mm. more before the point enters the aqueduct. It should be remembered that the needle does not enter in an exact vertical direction, but must descend somewhat obliquely toward the midline. This work was carried out under strict aseptic precautions, and about 1 c.c. of sterilized paraffin injected.

It is necessary to mention here that some authors speak of trephining as synonymous with decompression and therefore may attempt to explain the regularly occurring delay in the development of hydrocephalus in these animals as due to this opening in the skull. The trephine opening, however, was never more than 2 mm. in diameter, and the dura was never perforated except with the fairly thin needle of the paraffin injection syringe. It is a matter of surgical knowledge



Fig. 4.—Section of choked disk, left eye, Dog 6.

that the opening in the skull must be larger than that made by a common trephine when relief of pressure is sought by decompression, and in addition the dura must be incised.

To indicate fully the manner in which the experiments were carried on the following two are given in detail. These are typical, and an account of any of the others would be mere repetition.

Observation 2.—Oct. 10, 1916. Medium sized, black fox terrier. Ether anesthesia.

Ophthalmoscopic examination of fundus shows nothing abnormal. Vessels appear normal and optic disk is on same plane as the retina.

1:30 p. m. Small trephine opening made and 1 c.c. of paraffin injected into the aqueduct. Retinal vessels and disk show no change.

2 p. m. and 3 p. m. No changes noted.



October 11. Dog is lively and normal to all appearances. Ophthalmoscopic examination reveals no change from picture presented yesterday.

October 12. Dog is normal and active. The slight skin incision over the occipital protuberance has united. Suture clip is removed. The ophthalmoscope shows very prominent and tortuous retinal veins but no swelling of the optic disk.

October 13. Dog appears apathetic and refuses food. Fundus oculi show prominent and tortuous veins with disk swollen 2 D in left eye and a little more than 1 D in right eye.

October 14. No ocular examination made. Animal keeper reported that dog was apathetic and refused food.

October 15. Dog is extremely stuporous. Moves only when urged. Movements are spastic. Eyes show a distinct exophthalmos. Ophthalmoscope shows presence of retinal hemorrhages and a high choked disk in both eyes. Right eye 5 D; left eye 4 D. Animal is chloroformed.

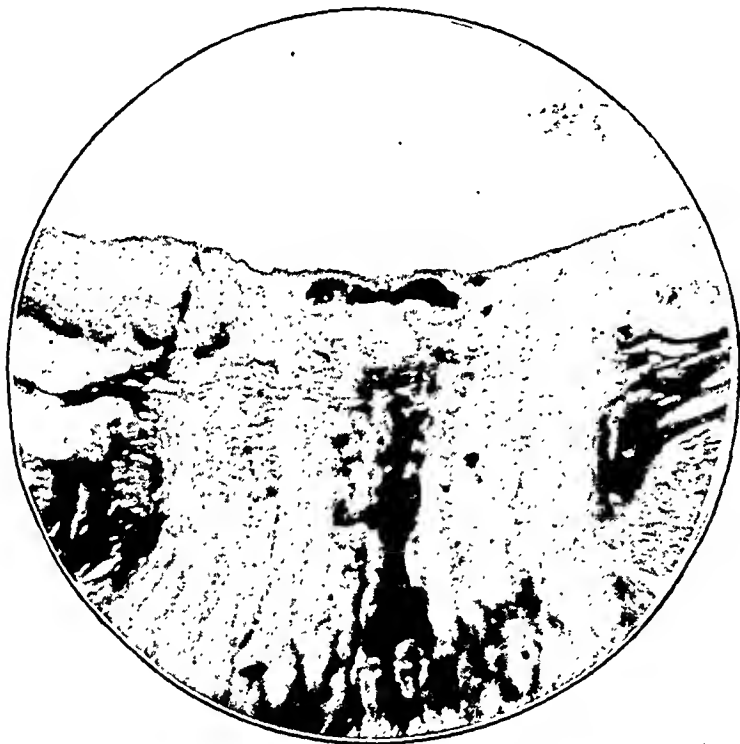


Fig. 5.—Section of choked disk, right eye, Dog 6.

Necropsy.—Removal of the occipital skull reveals a tense dura. On incision a clear fluid which is under considerable pressure escapes. The amount is slight. The brain sulci are indistinct and appear flattened from pressure against the dura.

The optic nerve is firmly lodged in the bony foramen. The sheath appears to have a larger than normal diameter, is sacculated and on incision fluid escapes from it. The eyes and optic nerves were fixed in Perenyi's fluid.

The brain was hardened in 10 per cent. formaldehyd solution and after several days division of it along the longitudinal fissure showed a small plug of paraffin lodged securely in the aqueduct and extending anteriorly into the third ventricle and posteriorly against the cerebellum as it arches over the fourth ventricle. No evidences of local inflammation are present.

The third and lateral ventricles are slightly distended but no prominent hydrocephalus exists. This is to some extent due to the shrinkage resulting from the fixation, as the brain now no longer bulges along the lateral ventricles as it did in the fresh state when an acute ventricular distention was present.

Histologic Observations.—Histologic examination of the eyes shows a distinct swelling of the disk, illustrated in Figures 2 and 3. Definite separation by edema of the nerve fibers as they pass through the disk and over the retina is apparent. No other inflammatory signs such as round cells are observed. Numerous extravasations of blood occur over the entire retina.

Observation 6.—Jan. 3, 1917. Small mongrel dog. Ether anesthesia.

Retinal vessels and disk are normal. The skull is trephined as usual and the aqueduct occluded. About 1 c.c. of paraffin is injected. This operation has no effect on the retina or disk.

January 4 to 7. Dog is lively, feeds well and appears normal in all respects.

January 8. Dog is listless, feeds poorly. Ophthalmoscopic examination shows tortuous and prominent retinal vessels. Disks are slightly swollen.

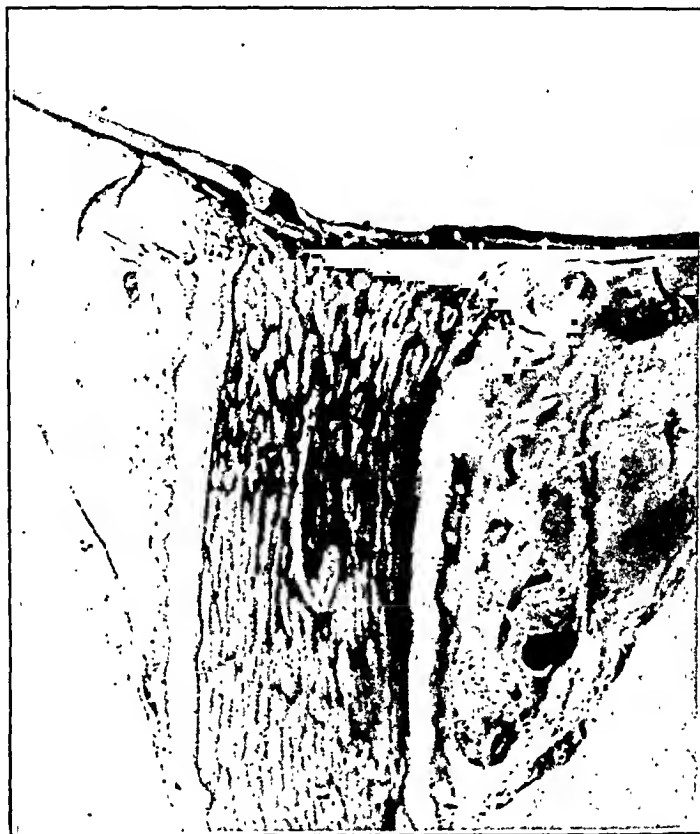


Fig. 6.—Section through the center of optic nerve and papilla from a dog killed three days after the aqueduct had been plugged. Vascular congestion of retina and dilatation of the dural sheath are present. The subarachnoid spaces are not distended. The venous engorgement, due to shrinkage in fixation, is not as prominent as it presented itself in the live animal.

January 9. No observations made.

January 10. Dog has a definite exophthalmos. Retinal vessels do not stand above retina with the prominence observed two days previously. Small hemorrhagic areas are scattered over entire retina. Left eye has a choked disk that measures 7 D.; right eye between 5 and 6 D. On this day the animal was extremely stuporous, refused to walk and when forced showed a marked spasticity. Later in the day he became comatose and was chloroformed.

Necropsy.—Both eyes and optic nerves were fixed immediately.



Opening the skull showed conditions identical with those observed in Dog 2. The brain was fixed in 10 per cent. formaldehyd solution and subsequent examination of it showed no variation in any important detail from the findings described in Observation 2.

Histologic Observations.—No marked variations in detail exist from those mentioned under Dog 2. The vascular congestion, with the wide spread edema and absence of round cells are the prominent features. Photomicrographs of both eyes and optic nerves are given in Figures 4 and 5. These photomicrographs are of the same magnification as that of the normal eye, Figure 1.

The foregoing two detailed accounts, for the sake of space, must suffice to illustrate the type of experiments carried on. However, out of a series of ten dogs, six developed the conditions mentioned within a period never shorter than three days nor longer than ten days after

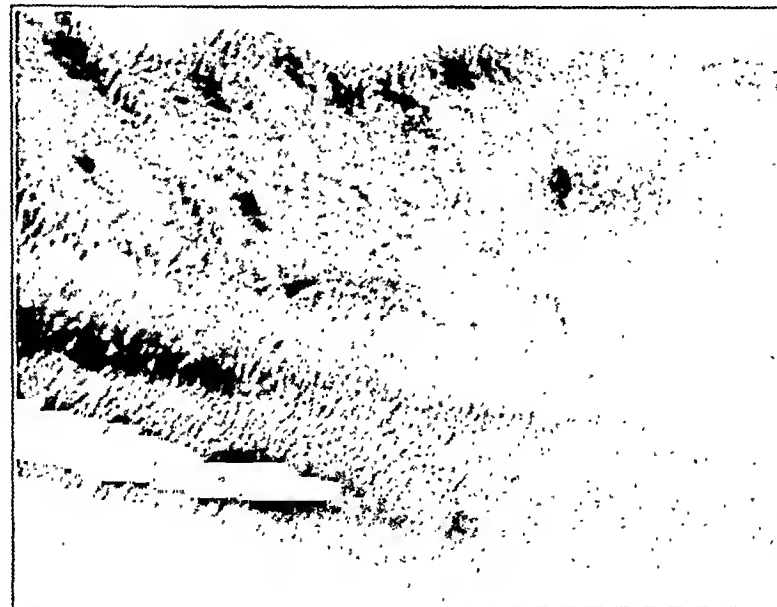


Fig. 7.—Moderate power photomicrograph of a choked disk retina to illustrate the extent of the edema among the nerve fibers. This is taken from the same respective location in the retina as Figure 8. Notice the difference in the thickness of the optic nerve fiber layer and the extent to which it is filled with edema. The internal limiting membrane is raised and in folds. Taken from right eye of Dog 4.

the aqueduct had been blocked. Necropsies on the four animals that did not develop choked disk showed that the aqueduct had not been completely occluded. This was due in two instances to an insufficient amount of paraffin, in another it had entered the third ventricle, and in the fourth it had lodged above the aqueduct.

It was noticed in every animal that developed an acute hydrocephalus that the first sign of an increased cerebral pressure was always a greater prominence of the retinal vessels, and especially the veins. This was observed as early as the second day, more frequently, however, on the third day, and always from twelve to twenty-four

hours before any swelling of the optic disk appeared. As these vessels became increasingly prominent their tortuosity increased and stood out boldly above the surface of the retina.

On account of these observations several animals were killed within three or four days after the aqueduct had been plugged at a time when the retinal venous engorgement was prominent, but signs of actual swelling of the disk did not as yet exist. This was done to determine whether such venous engorgement could possibly be associated with some changes within the sheath of the optic nerve itself.

The necropsies on these animals gave uniform results. In all a mild degree of hydrocephalus existed. The brain was fairly tense, as though slight pressure was exerted from within. The sulci, however, were still plainly marked and the brain was not pressed so firmly against the dura as in the case of those animals that were allowed to develop a severe hydrocephalus.

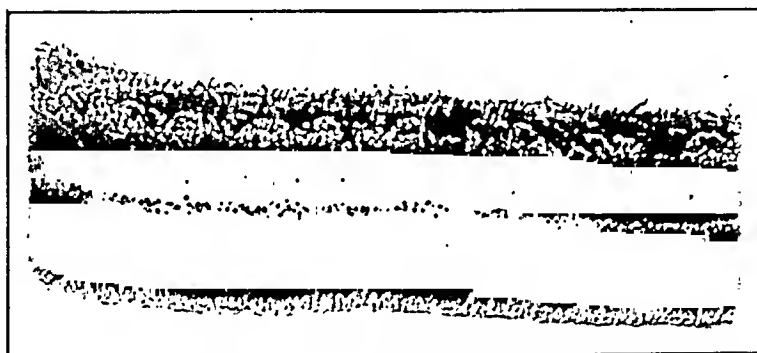


Fig. 8.—Photomicrograph of a normal retina to contrast with Figure 7. The magnification is the same. Note the difference in the thickness of the nerve fiber layer.

Histologic examination of the eyes shows prominent retinal vessels; evidence of retinal hemorrhage is absent. Swelling of the disk is not apparent, nor can traces of edema be found among the optic fibers of the retina. The dural portion of the optic sheath is moderately distended, but sacculations, such as occurred in the severe grades of hydrocephalus, are absent, nor are there indications of distended sub-arachnoid spaces, Figure 6.

It is apparent from these experiments that a condition of hydrocephalus can be induced in an adult dog by plugging the aqueduct of Sylvius with paraffin, and that where such condition becomes established, choked disk will result. But it will also be noticed that the development of such an hydrocephalic condition is a gradual process which requires at least seventy-two hours before it will manifest itself through a retinal venous engorgement. In none of these animals did this process develop into a severe hydrocephalus, associated with



choked disk and a subsequent comatose condition, in less than ninety-six hours. These results are at variance with the observations of Frazier and Peet¹⁹ who induced the same condition within a period of twenty-four to thirty-six hours by injecting aleuronat suspension into the third ventricle and placing a gauze plug against the lower end of the aqueduct.

The histologic preparations of these eyes show that the disk undergoes severe changes after the animal has suffered from hydrocephalus for a period of three to five days. An edema is present not only in the disk, but throughout the entire nerve fiber layer as it spreads over the retina. The fibers are separated and the spaces that formed are filled with fluid. In the advanced stages a stretching and separation of the fibers extends even into the anterior layers of the lamina cribrosa. As a result of this infiltration of fluid the disk is uniformly increased in size and spreads out over the retina.



Fig. 9.—Coronal section of two forebrains. A, hydrocephalic brain to contrast with B, which is a normal dog's brain; seven-eighths natural size.

This widespread edema through the nerve fibers of the disk and retina causes considerable disturbance. Frequently the course of these fibers becomes S-shaped in outline. This is a feature to which Paton and Holmes have already called attention in their observations on clinical material.

The histologic findings in these experiments agree with those obtained by other workers. Round cells, such as would be expected to be present were this condition a true inflammation, are absent. Instead, a clear noncellular fluid is easily demonstrated between the fibers (Fig. 7), giving in all respects the picture of a simple edema. In these hydrocephalic dogs a choked disk with the histologic picture of a true inflammation did not exist, and it may therefore be well assumed that it was noninflammatory in origin.

19. Frazier and Peet: *Am. J. Physiol.* 35:268, 1914.

It was noted in every instance where a pronounced choked disk occurred that at least a moderate ventricular distention (Fig. 9) was present. This distention was never extreme, which may readily be explained on the basis of the rigidity of the skull.

Recently Tilney²⁰ called attention to the presence of a small canal extending out from the third ventricle above the optic nerve and chiasma. This tubular extension from the third ventricle persists into adult animals only in its proximal portion, and according to Tilney extends along the nerve for a distance of 0.75 mm.

It is Tilney's opinion that this supra-optic canal is of clinical significance²¹ in connection with choked disk where there is an accumulation and retention of fluid in the forebrain ventricles. With this idea in mind several of these moderately distended brains were sectioned serially through the region of the optic chiasma in the hope that the ventricular dilatation had caused a distention of the supraoptic canal. Nothing definite could be established, on the basis of this material, at least. In consequence the hypothesis that choked disk is possibly the result of distention and transmission of fluid through a possible supra-optic duct finds no corroboration here.

Attention has already been called to the uniform occurrence of a moderately distended dural sheath space (Fig. 6) at a time when nothing more than a retinal venous engorgement marked the development of an internal hydrocephalus. As this last condition progressed the sheath distention became more prominent until it showed frequent sacculations (Fig. 12) and involved the subarachnoid spaces. This same condition has been observed on clinical material by Paton and Holmes in England, and by Cushing and Bordley in this country. It is evident, therefore, that hydrocephalus in a dog will lead to the same conditions that present themselves in man suffering from ventricular distention as a result of tumor growth or of some other cause.

With this established, no great recognition must be given to the anatomic difference present in the circulation of the eye of man and that of the dog. By many this has been held as sufficiently important to vitiate the application to man of the experimental results obtained on dogs. Particularly so, since in the dog only a very small amount of blood returns from the eye into the cavernous sinus, leaving the greatest portion to flow through the vorticose and anterior ciliary veins into the external jugular. In consequence, the venous circulation of the dog's eye is essentially extracranial, while in man it is primarily an intracranial return system through the central vein into the cavernous sinus. True, an anastomosis occurs between the central and

20. Tilney: *J. Comp. Neurol.* 25:213, 1915.

21. Tilney: *Anat. Record* 10:250, 1916.





Fig. 10.—A graphic representation of the effect of increased intracranial pressure on the venous and arterial pressure, on respiration and the heart rate. The animal was under ether anesthesia only. Observation made on Dog 6, Series II.

ophthalmic veins, which provides, however, only for an emergency flow through the facial into the external jugular. Due consideration of these enumerated differences, combined with a recognition of the similarity of optic changes produced in man and in dogs by an hydrocephalus, will lead to the conclusion that no great importance can be ascribed to the local anatomy of the circulation of the eyes as a causative factor in the origin of choked disk.

That the physiology of that circulation is, however, a very important factor in the production of optic disk edema is constantly indicated by several conditions: These are, first, the early and uniform appearance of a retinal venous engorgement, which occurs equally in animals with an intracranial or extracranial return circulation; second, the extension of this venous engorgement to the peripheral system so that it becomes especially marked in the conjunctival and anterior ciliary veins; third, the development of a distinct and frequently an extreme exophthalmos, accompanied by a marked edema of the tissues within the optic orbit; lastly, by the results of physiologic and pharmacologic experiments undertaken in order to control these observations.

These experiments were carried out on eleven dogs under the direction and kind assistance of Professor Becht of the pharmacology department. I take great pleasure in acknowledging my thanks to Professor Becht for his interest in this phase of the work and his personal assistance in performing many of the following experiments.

An acute hydrocephalus was produced in these animals by allowing fluid under pressure to enter the subdural space. This method needs no further description, since it has been used by many experimenters. The typical notes of such an experiment are as follow:

Observation 4.—Ether anesthesia. Brown fox terrier.

1 p. m. The skull was trephined and a tightly fitting cannula placed over right hemisphere and connected with pressure bottle filled with warm normal saline solution. Tubing from the pressure bottle was also connected by means of a "T" to a mercury manometer to record the pressure. The right carotid artery was exposed, a cannula inserted and connected with another mercury manometer to obtain records of the blood pressure and heart rate. The axillary vein was next exposed and the venous pressure taken from here by means of a manometer containing sodium carbonate solution. From this the venous pressure could be read off directly, but to obtain a permanent and graphic record the manometer was connected to a tambour and tracings were made of this simultaneously with the blood and intracranial pressure.

1:40 p. m. Examination of the eyes shows nothing abnormal. The retinal vessels are normal in size and color. The disk is on the same plane with the retina.

1:50 p. m. Fluid is allowed to enter the subdural space. The pressure was gradually raised to equal that of the arterial pressure. Within a minute the effect of this became visible in a marked slowing of the heart, a transitory rise and then a fall in blood pressure. This was accompanied by a marked rise in venous pressure. The intracranial pressure was now maintained at this level. Observations on the fundus oculi showed veins which were quite

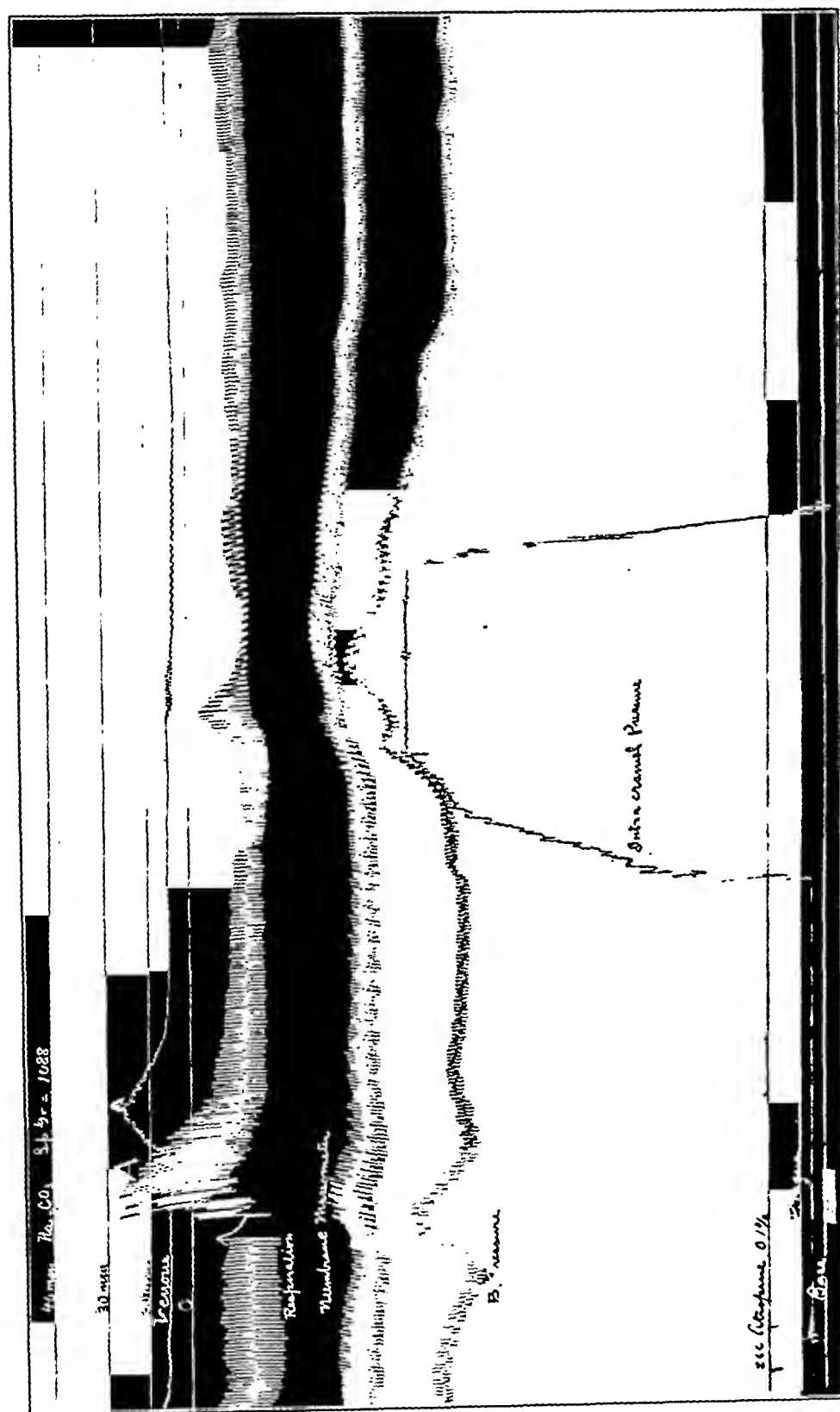


Fig. 11.—A graphic illustration of the failure to obtain any rise in venous pressure following an increased intracranial pressure, after the animal had received 2 c.c. of a 0.1 per cent. solution atropin sulphate. The rise in venous pressure at A is due to electrical stimulation of the vagus within a minute after the atropin had been injected.

tortuous and very prominent, but no signs of a swollen disk presented themselves.

Respiration stopped for a period of a minute and then broke through again. The venous pressure dropped slightly but was still high. Blood pressure remained decreased.

2:10 p. m. Venous pressure is still high; 45 mm. of water. Retinal veins are tortuous and disks are swollen in both eyes.

2:30 p. m. Intracranial pressure is still maintained at the former level. Respiration is slow. Blood pressure is decreased but venous pressure rises higher. Now up to 60 mm. of water. Both eyes show a distinct swollen disk, about 3 D. in left and 2 D. in right. A definite exophthalmos is present. Conjunctival veins are swollen. Also the anterior ciliary. The conjunctivae are edematous. The pupils are widely dilated. Pressure on the eyeball reduces the tortuosity and size of the veins, but no decided influence on the disk is observed.

3 p. m. Venous pressure is still high. No further eye changes but the exophthalmos has become most pronounced. Both eyes bulge far beyond their orbits. A marked palpable increase in intra-ocular tension exists.

3:30 p. m. Intracranial pressure is maintained at the original level of 140 mm. Hg. Venous pressure rises rapidly, while there is an equally rapid drop in arterial pressure. Respiration is very slow and failing.

3:45 p. m. Respiration has failed and heart stops beating within a minute. Both eyes and optic nerves are fixed immediately for histologic study.

As the intracranial pressure approached or went above the height of the blood pressure in these animals a drop in the heart rate and of the blood pressure and a rise in venous pressure occurred. This rise in venous pressure was not a local one, but was general, as is indicated by the identical results, whether the pressure was taken from the axillary or from the femoral vein.

A study of the tracings of this series of experiments showed that the increased intracranial pressure always resulted in a marked slowing of the heart rate. This slowing of the heart rate was uniformly accompanied by a progressive rise in venous pressure and subsequent to this definite signs of choked disk would develop.

On the basis of these observations a second type of experiments was decided on. In these the inhibitory action of the vagus on the heart was removed by atropin in order to determine whether the prevention of a high venous pressure in the presence of an increased intracranial pressure might possibly also prevent the formation of a choked disk.

A series of three such experiments was conducted. These in the details of procedure were duplicates of the foregoing except that the animals were thoroughly atropinized by the hypodermic injection of 5 c.c. of a 0.1 per cent. solution of atropin sulphate.

In these animals the intracranial pressure could easily be raised to an equal level with that of the arterial pressure and even above without a resultant rise in venous pressure. Instead of a rise in venous pressure there followed, however, an increase in heart rate and always a rise in arterial pressure.



Observations made on the eyegrounds of these atropinized animals during the course of the experiments showed that the continued high intracranial pressure had no effect on changing the appearance of the retinal veins or in producing a choked disk. No sign of exophthalmos ever developed, nor were there any visibly congested anterior ciliary or conjunctival veins in any of these atropinized animals.

The high intracranial pressure was maintained for as long a period as three and one-half hours in two of these dogs, and no variation from the normal occurred in their retinal veins or in the disk itself until just before their death, when the heart action became feeble. During the last half hour a slight retinal venous engorgement became apparent, but at no time did an actual choked disk develop which was visible ophthalmoscopically or afterwards in the histologic preparations of the eyes from these dogs.

TABLE 1.—TO ILLUSTRATE THE DIFFERENCE IN THE EFFECT OF INCREASED INTRACRANIAL PRESSURE ON THE VENOUS AND ARTERIAL PRESSURE OF THREE ATROPIN-FREE AGAINST THREE HEAVILY ATROPINIZED DOGS *

Dogs: Atropin-free				Dogs: Atropinized with 5 C.c. of A 0.1% Solution			
Dog No.	C. S. F. P., Mm. Hg	Venous P., Mm. H ₂ O	Arterial P., Mm. Hg	Dog No.	C. S. F. P., Mm. Hg	Venous P., Mm. H ₂ O	Arterial P., Mm. Hg
2	Normal	2.10	114.0	7	Normal	3.4	130.0
	+156	70.0	80.0		+128	3.2	148.0
3	Normal	4.0	112.0	8	Normal	4.1	132.0
	+160	52.0	88.0		+148	3.8	140.0
4	Normal	4.5	116.0	9	Normal	1.4	120.0
	+126	65.0	120.0		+210	1.8	206.0

* Dogs 1 and 5 are not included in this series because of mechanical errors which occurred during the experiment. Dog 6 is listed separately in Table 2 and Dogs 10 and 11 in Table 3.

Table 1 will illustrate the marked difference in effect of increased intracranial pressure on the arterial and venous pressures when the accentuated inhibitory action of the vagus on the heart is allowed to act and when the same is removed by the use of atropin. The difference in the venous pressures is extremely marked and to bring this particularly to the attention of the reader a summary of the various tracings from six experiments is given in the table.

It must suffice at this time to draw the attention of the reader to a close comparison of the figures given in Table 1. Their full significance will be discussed later along with the results of experiments in which the effect of increased intracranial pressure was studied in animals which were for the first part of the experiments atropin-free

and for the remaining part heavily atropinized. The conduct of these experiments was the same as that of the foregoing, except that after a complete record of the effect of increased intracranial pressure exerted for only a brief period had been obtained this same animal was given atropin and the intracranial pressure was again raised to the former level. A graphic record of this is given in Figures 10 and 11. This experiment represents a combination of the former two types the results of which are given in Table 1, and therefore Figures 10 and 11 also serve to illustrate these graphically.

For comparing the effect of such increased intracranial pressure on the arterial and venous pressure of the same dog when atropin free and when atropinized, Table 2 is given. It is based on the results from Dog 2, which are graphically given in Figures 10 and 11.

TABLE 2.—BASED ON EXPERIMENTAL RESULTS FROM DOG 6, ILLUSTRATING THE INFLUENCE OF ATROPIN ON THE EFFECT OF INCREASED INTRACRANIAL PRESSURE
Ether Anesthesia

Before Atropin					After 2 C.c. of 0.1 per Cent. Solution of Atropin				
Intra-cranial Pres-sure	Venous Pres-sure, Mm. of H ₂ O	Blood Pres-sure, Mm. of Hg	Heart Rate, per Min.	Respir-atory Rate, per Min.	Intra-cranial Pres-sure	Venous Pres-sure, Mm. of H ₂ O	Blood Pres-sure, Mm. of Hg	Heart Rate, per Min.	Respir-atory Rate, per Min.
Normal	4.1	132	104	60	Normal	4.05	142	90	45
+142 mm.	51.56*	108	30	10	+154 mm.	4.0*	178	110	24
Normal	4.3	134	85	54	Normal	3.5	138	92	45

* Contrast venous pressure before atropin is given with the same after atropin.

A full discussion of all of the figures in this table is not necessary. It is important to notice, however, that in this animal, as also in the three listed in Table 1 which were atropin free, the arterial and venous pressures undergo a marked change. Reference to Figure 10 shows that there is first a slowing of the heart rate, and this is soon accompanied by a fall in arterial pressure which is preliminary to a rise in venous pressure. Release of the intracranial pressure results soon in the former vascular equilibrium.

Contrast these findings now with those given in the last half of Table 2 and illustrated graphically in Figure 11 as representing the effect of even a higher increase in intracranial pressure on the heart rate and on the arterial and venous pressures. Here the heart rate steadily increased, the arterial pressure rose and the venous pressure remained practically the same. If any favoritism was shown in the way of a less high intracranial pressure it was in this as in the other dogs listed in Table 1 for those without atropin.

Now, inasmuch as none of these atropinized dogs showed any signs of a choked disk, whereas it was uniformly obtained in the atropin-free dogs suffering from similar or less pressure, it does not seem too much to say that the existence of a high venous pressure is an important factor in the formation of optic disk edema. This statement is based on the fact that in these experimental animals which were subjected to an increased intracranial pressure and in which by the use of atropin the inhibitory action of the vagus was removed, a failure in the production of a high venous pressure and of any visible evidence either ophthalmoscopically or histologically of a choked disk resulted; while, on the other hand, in those animals in which the vagus action was not removed by atropin such, or even less, increased intracranial pressure uniformly resulted in a high venous pressure and pronounced optic disk edema.

TABLE 3.—OPHTHALMOSCOPIC OBSERVATIONS ON DOGS 10 AND 11 *

Dog 10 Without Atropin	Dog 11 Atropinized
1:30 p. m. Retinal vessels and optic disk normal; pulse 102	R. V. and optic disk are negative; pulse 120
1:40 p. m. Pressure applied to both dogs	
1:50 p. m. R. V.† quite tortuous and raised; no optic disk edema; pulse +90	R. V. are negative; pulse 130
2:10 p. m. R. V. very tortuous; disk appears slightly changed but no definite swelling; pulse 80	No changes; pulse 150
2:30 p. m. Choked disk in both eyes; right eye 2 D.; left eye 1 D.; pulse 72	No changes; pulse 150
3:00 p. m. Choked disk has increased on both sides to 3 D.; beginning exophthalmos present; pulse 70	No changes; pulse 140
3:30 p. m. Disk now raised 4 D. both eyes; marked exophthalmos	No changes; pulse 126; no exophthalmos
4:00 p. m. No changes from foregoing; pulse 68	No changes; pulse 120

* The intracranial pressure was raised within ten minutes to 140 mm. of Hg and maintained there for four hours.

† R. V. = retinal vessels.

It is apparent, then, that two factors are necessary in the production of choked disk. These are, first, an increase in intracranial pressure, and second, an increased venous pressure.

But as a further control and in order more fully, if possible, to establish the fact that the foregoing factors are not capable of singly causing the formation of an optic disk edema, the following experiment was performed.

Two male fox terrier dogs of as near as possible the same weight were subjected to the same intracranial pressure for a period of four hours. A common pressure flask was used for the two dogs. One rubber tube led from the bottle to within 12 inches of the dogs' heads. Here a "T" tube was inserted and connections were made with the cannulas by two equally long pieces of pressure tubing. Tracing of the arterial and venous pressures were not

taken in order to obviate the necessity of possibly vitiating the results from trauma to the animals. These animals are Dogs 10 and 11. Dog 10 was simply anesthetized with ether while his partner, Dog 11, received 5 c.c. of a 0.1 per cent. solution of atropin hypodermically before the ether anesthesia was begun. Table 3 is a record of the observations made on both of these animals.

No further eye changes developed within the next hour and a half in Dog 10. Dog 11 began to show an increased tortuosity of the retinal veins at 5:15 p. m., but by 5:30 p. m., when both dogs were killed, no evidence of optic disk edema or of exophthalmos was present in this animal.

The difference in the effect of this long continued high intracranial pressure on the atropin-free and on the atropinized dog is illustrated even better in the accompanying Figure 12; A, represents the degree of choked disk developed in the right eye of Dog 10, and B, is from the right eye of Dog 11. Both A and B show a marked dilatation of the optic nerve sheath. This was much more pronounced when the tissues were fresh and has decreased as a result of shrinkage during fixation and in the process of making the sections. In the illustration from the eye of Dog 10 there is shown a pronounced choked disk, which contrasts sharply with that from Dog 11, in which the disk is practically normal. A slight deviation from the normal consists here in the well filled retinal veins. As has been stated, however, this congestion occurred during the last ten minutes just previous to the animal's death, when the heart action suddenly weakened, along with respiratory failure. Microscopic examination of the sections from the eyes of Dog 10 shows that the optic nerve fibers are separated and that a finely granular substance fills the interstices, duplicating in all respects the picture obtained in the choked disk that developed in response to the presence of a hydrocephalus from blocking the aqueduct of Sylvius. No such findings are present in the sections from Dog 11.

Consideration of the experimental evidence gathered in this work leads to the conclusion that the absence of a high venous pressure in the presence of an increased intracranial pressure is sufficient to prevent the formation of a choked disk. Logically, then, the next question must be, Can a venous stasis alone cause an optic disk edema?

This question has had to be answered in the negative by various investigators.

The work of Uhthoff and of Cushing and Bordley needs to be especially mentioned in this connection. In order, however, to be able to observe personally what changes do occur when a rise in venous pressure alone is brought about, both the external jugular veins of a small mongrel dog were ligated. Within a few minutes his facial veins filled up and became prominent. Likewise his conjunctival and

anterior ciliary veins. The ophthalmoscope showed an increased tortuosity present in the retinal veins but no sign of any optic disk edema, even an hour later. A further examination several hours later showed still an increased prominence of the retinal veins, but no choked disk. After twenty-four hours the retinal vessels appeared normal again and no further changes occurred during forty-eight hours, after which time the ligation around both jugulars was removed. The result was entirely negative as far as the production of a choked disk was concerned. The effect, then, of a venous stasis alone is well summarized by Cushing. He says: "Simple venous stasis in the retinal veins fails to produce anything more than the congestive features of venous engorgement which accompanies a choked disk and never leads directly to a definite edema of the papilla."

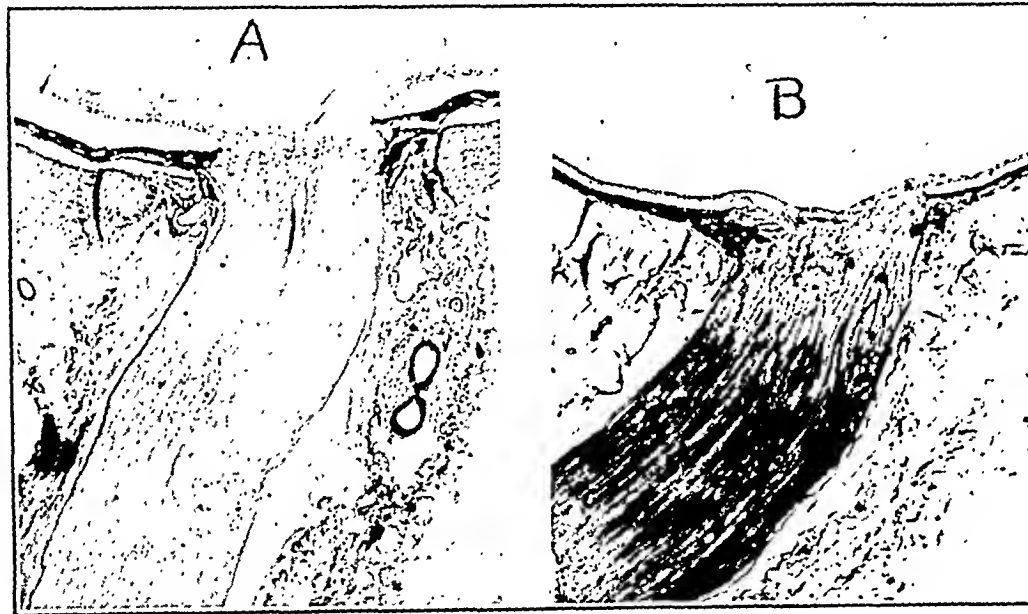


Fig. 12.—Photomicrograph of sections from the right eyes of Dogs 10 and 11, Series II, to show the different effect from the equally increased intracranial pressure in an atropin-free and a heavily atropinized dog.

DISCUSSION

The purpose of the foregoing has been to establish clearly that the origin of choked disk is dependent on a combination of two factors. These are, first, an increased intracranial pressure, and second, an increased venous pressure. This second factor in all probability is due to the presence of the first, but if proper precautions are taken a high venous pressure can be prevented, and with it the formation of an optic disk edema.

Recognition of these facts will readily explain the almost uniform occurrence of choked disk in certain pathologic conditions in man. Thus, in cases of brain tumor or of chronic brain abscess, or, again,

in the hemorrhagic type of pachymeningitis, conditions are present that are almost uniformly accompanied by choked disk. And these cases all show a bradycardia and an increased cerebrospinal fluid pressure. Often the bradycardia presages the advent of the condition. Here often the pulse rate drops to 45 or 50 per minute and with a low arterial pressure such a pulse rate must mean a high venous pressure. These are the types of cases in which both conditions necessary for the formation of a choked disk are present, and, as a matter of common observation, the latter does develop much more frequently than not.

On the other hand, it was early recognized by Gowers that in advanced cases of acute miliary tuberculosis the pulse rate may be extremely low and be accompanied by a low arterial pressure and still these patients never develop more than the congestive features of choked disk. An actual edema never develops. Here the other necessary factor, the increased intracranial pressure, is absent.

Again, the increased intracranial pressure may be present as it undoubtedly is in the so-called condition of "wet-brain" in delirium tremens and still with the accompanying high pulse rate and arterial pressure and failure of development of high venous pressure no choked disk develops.

Optic disk edema develops in man where an increased cerebrospinal fluid pressure and a slow heart rate exist, as can be observed clinically. In these experimental hydrocephalic dogs a condition of high cerebrospinal fluid pressure plus a venous congestion leads to a similar picture. Then, if to a recognition of these two factors that of the lymphatic drainage from the retina, disk and nerve are added, all necessary data for the explanation of the origin of choked disk are at hand. As a result of the engorgement of the retinal veins due to the high venous pressure, an excessive transudate of lymph into the tissues of the retina and disk occurs. Since no proper lymph vessels exist, the tissues distend (Fig. 7) until the pressure exerted in the stretching comes to equal that which obstructs the drainage. The obstruction is the pressure of the cerebrospinal fluid within the sheath lymphatic spaces transmitted from the subarachnoid space of the brain. If this pressure is removed as in ordinary decompression operations the edema in the disk disappears because lymph drainage is again established. As long, however, as the obstructive pressure is greater or maintains a balance with the lymph pressure exerted in the stretching of the retinal tissues and disk, an optic disk edema will continue to exist.

That the increased venous pressure as manifested by an engorgement of the retinal veins cannot be due to a local cause such as direct pressure of the fluid within the optic sheath pressing on the nerve



structure, as was argued by Manz, is definitely proved by these experiments. These show that such retinal venous prominence is simply a local manifestation of a general high venous pressure which manifests itself in all the veins. Whether this high venous pressure is entirely due to the accentuated inhibitory action of the vagus consequent to central stimulation from the high cerebrospinal fluid pressure may be a question open for further investigation. The fact remains, however, that if such inhibitory action is removed by the use of atropin a high intracranial pressure is insufficient to produce a choked disk.

Nor can it any longer be said that the theory of Schmidt-Rimpler is a sufficient explanation. If, according to his suggestion, it were so simple a matter as a direct driving of cerebrospinal fluid through the lamina cribrosa with the consequence of an edematous infiltration of the nerve head, then a choked disk would develop equally well in animals with a normal or with a high venous pressure. But such has not occurred in these experiments. By the use of atropin the venous pressure has been kept normal, and in these cases when an increased intracranial pressure was induced beyond that, even, which in the animals without atropin caused a pronounced choked disk, no optic disk changes occurred.

SUMMARY

To summarize the results of these experiments it may be said:

1. The production of hydrocephalus in dogs is accompanied by a distended optic sheath, hemorrhages and engorgement of the retinal veins and an edematous swelling of the nerve head, thus presenting features which characterize choked disk in man.
2. The introduction of fluid under tension into the subdural space will also produce a like picture.
3. The introduction of fluid under tension into the subdural spaces in a dog that is thoroughly atropinized will lead to nothing further than just the congestive features of choked disk, and this only after a long period of sustained high intracranial pressure.
4. A venous stasis produced by ligation of the external jugular is insufficient to cause any optic disk changes.
5. The production of choked disk in cases of hydrocephalus is not dependent on the presence of inflammatory factors but arises mechanically as a result of a high venous pressure and an obstructed lymph drainage, both caused by the primary factor, the increased intracranial pressure.

THE TREATMENT OF BRONCHIAL ASTHMA WITH VACCINES *

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In a recent article¹ it was shown that 191, or 48 per cent., of patients with bronchial asthma were sensitive to some type of protein. In a more recent article² the results of treatment with proteins of 100 of the sensitive patients was given; this 100 included only those patients who were sensitive to the proteins of animal hair and emanations and of food. The present paper concerns those patients who were treated with vaccines and represents a total of 178 individuals. Twenty-eight of these patients were sensitive to bacterial proteins, and therefore these patients were treated with vaccines of the organisms to which they were sensitive. The remaining 150 patients included in this paper were not sensitive to any protein with which they were tested. Since these nonsensitive patients are a part of the whole series of 400 cases, 48 per cent. of whom were found to be sensitive, it may be assumed, as shown in the previous paper, that these nonsensitive patients were tested with a sufficient number of proteins to justify the statement that they belong in the nonsensitive group. Therefore, this paper comprises all of those patients in the series of 400 studied who were sensitive to and treated with bacteria (28 in all), and all of those nonsensitive patients who had a reasonable amount of treatment (150 in all).

Since the aim of these studies,³ of which this article is a part, has been to determine the cause, and consequently the treatment, of bronchial asthma, the patients represented in this article have been treated in various ways; an outline of the various methods of treatment follows. The first part of the paper concerns those patients who were sensitive to bacterial proteins, and, as already mentioned, these patients were treated with vaccines of the bacteria to which they were

* From the Medical Clinic of the Peter Bent Brigham Hospital.

1. Walker, I. C.: A Clinical Study of 400 Patients with Bronchial Asthma, Boston M. and S. J. **179**:288, 1918.

2. Walker, I. C.: Treatment of Bronchial Asthma with Proteins, Archives Int. Med. **22**:466, 1918.

3. Studies on bronchial asthma were made possible through a gift by Mr. Charles F. Choate, Jr., of Boston to the Peter Bent Brigham Hospital. A complete list of the papers is given with the article in Arch. Int. Med. **22**:466, 1918.

sensitive. Since the other patients were not sensitive to proteins, they were thought to be of an infectious type and the infection was considered to be in the respiratory tract. Therefore, vaccines were made from the organisms found in the patients' sputum or nasal secretions. Since these sources produced such a wide range of bacteria, it was thought best and simplest first to find out what part those organisms which only grow on plain agar might play in the cause of bronchial asthma; the results of this work are given in the second part of the article. We were next interested in the part those organisms which grow only in dextrose bouillon and not in plain agar might play in the cause of bronchial asthma; thus, the third part of this article deals chiefly with streptococci and pneumococci. It was learned that some patients were relieved of asthma by plain agar vaccines and that others were relieved by bouillon vaccines, but still there were many in each group that were not relieved. Therefore, a series of patients were treated in both ways; that is, some who were not relieved by vaccines made from growing the sputum on plain agar were then treated with vaccines made by growing the sputum in dextrose bouillon, and vice versa; also blood agar plates were usually made from a shaken emulsion of the sputum in dextrose bouillon in order to determine the predominating organism and to identify the various types of bacteria. Thus the fourth part of the paper deals with the treatment by vaccines which were made both ways. In other papers we have already called attention to the fact that the nonsensitive as well as the sensitive patients with bronchial asthma may have asthmatic attacks throughout the year or only at various times or seasons of the year. It is obvious that it is impossible to prognosticate results from vaccine treatment in patients who have asthma only for a period of a month or six weeks once or twice a year, as is the case with some patients who have an early spring attack or a late fall attack or two such attacks; therefore, patients who have such limited asthma are not included at all in this paper, although there is evidence that bacteria are frequently the cause of such asthma. The method of treatment which has already been outlined in this paper concerns only those patients who have either continuous or frequently repeated attacks of asthma throughout the year, or those who have asthma from early fall throughout the winter and early spring; that is to say, they have asthma throughout the greater part of the year. Even in these latter cases one must be very cautious in interpreting benefit from treatment since a mild winter or an early spring might account for the improvement in the asthma, and for this reason we have attempted to be very conservative in our results. There is, however, still another type of asthma to which attention should be called since it is an entity and closely

simulates asthma caused by pollens. This is a nonsensitive type of summer asthma caused by bacteria, and it is usually confined to the months of late May, June, July and early August, therefore closely simulating the early pollen asthma. A small series of this summer nonsensitive type of asthma will be presented in this article. Finally, attention will be called to specificity among bacteria and proteins in the treatment of bronchial asthma, and proof of such specificity, including the use of intravenous typhoid vaccine and subcutaneous peptone, will be given.

Patients sensitive to bacterial protein and treated with vaccines.—

As has been said, twenty-eight patients were sensitive to and treated with bacteria. In addition to these there were eleven other patients who were sensitive to bacterial proteins, but as they were also sensitive to other proteins, these patients were included in the preceding article,² and therefore will not be discussed here. Two other patients are not discussed here because they were not seen after their first visit. Therefore, in the total of 400 patients on which these studies have been based, forty-one, or 10 per cent., were sensitive to bacterial proteins. Two different standards must be considered when reading skin tests with bacterial proteins. One type of positive reaction is an urticarial wheal measuring at least 0.25 to 0.5 cm. in diameter, which appears within one-half hour, and the other type is a delayed reaction which occurs hours later, and the next day the site of the inoculation is inflamed, hot, and elevated, and resembles an infection.

The treatment of the twenty-eight patients who were sensitive to and treated with bacteria consisted of either stock or autogenous vaccines of those bacteria to which they were sensitive. Treatment was given with the whole killed bacteria in the form of a vaccine, because by so doing the patient would be apt both to acquire an immunity to the bacteria and become desensitized to the protein of the bacteria, whereas treatment with the protein of the bacteria alone would only desensitize and not immunize; in other words, treatment with the protein alone simply protects the patients against bacterial protein, but as the bacteria are constantly present, the infection may at any time become so great as to undo suddenly what has been accomplished in the way of desensitization. A parallel instance is that of attempting to desensitize pollen cases while the patients are being exposed to the pollen, or of attempting to desensitize a wheat case while the patient is eating wheat. Treatment with vaccines of the bacteria to which the patient is sensitive both immunizes and desensitizes at the same time; thus protection against living bacteria parallels desensitization. It seemed to make no difference whether the vaccines

were stock or autogenous. A detailed discussion of the skin test and treatment with bacteria was presented in Studies III⁴ and XIV.⁵

A discussion of the twenty-eight patients who were sensitive to and treated with bacteria follows. Seventeen patients were sensitive to and treated with *Staphylococcus pyogenes aureus*; ten were relieved of asthma, six were markedly improved and one was not benefited at all. One patient was sensitive to and relieved by treatment with both *S. pyogenes aureus* and *albus*. Two patients were sensitive to both *S. pyogenes aureus* and *Streptococcus hemolysans*, and both were relieved by treatment with *S. hemolysans*; one was markedly improved by *S. pyogenes aureus* before treatment was begun with *S. hemolysans* and the other was not treated with *S. pyogenes aureus*. One patient who was sensitive to both *S. pyogenes aureus* and diphtheroid was markedly improved by *S. pyogenes aureus* vaccine and was later relieved of asthma by diphtheroid vaccines. Two patients who were sensitive to only *S. pyogenes albus* were relieved by treatment with this organism. One patient who was sensitive to both *S. pyogenes albus* and *S. pyogenes*, was markedly improved by *S. pyogenes albus* vaccine and was later relieved of asthma by *S. pyogenes* vaccine. Three patients were sensitive to the protein of *S. hemolysans* alone, and treatment with vaccine of this organism relieved the asthma. The remaining patient in this group of twenty-eight was sensitive to both *S. hemolysans* and *S. viridans*, and treatment with vaccines of both organisms relieved the asthma. Therefore, among the twenty-eight patients who were sensitive to and treated with bacteria, there was only one failure and six others who were not relieved but were markedly improved; these seven were sensitive to and treated with *S. pyogenes aureus*. There were no failures among those who were sensitive to and treated with the other bacteria, probably because they were not so frequent. In other words, 75 per cent. of the patients who were sensitive to and treated with bacterial proteins were relieved of asthma; it is interesting that these results are the same as were obtained by the treatment of patients with other proteins to which they were sensitive. (See previous article.)

The age of onset and the duration of asthma in the twenty-eight patients who were sensitive to and treated with bacteria follows: Three patients began to have asthma between the ages of 1 and 5; two of these who had had asthma for 5 and 20 years, respectively, were relieved, and the other one who was not benefited had had asthma for 7 years. Three began to have asthma between the ages of 5 and 10; all three were relieved and the duration of asthma in each case

4. Study III, Jour. Med. Research 35:487, 1917.

5. Study XIV, Jour. Med. Research 36:423, 1917.

was 2, 10 and 12 years. Five patients began to have asthma between the ages of 10 and 20; one who had had asthma for only one year was markedly improved, and the other four who had had asthma for 9, 13, 19 and 25 years, respectively, were relieved. Five patients began asthma between the ages of 20 and 30; all of these were relieved and the duration of asthma in these was 1, 4, 5, 5 and 10 years, respectively. Ten patients had their first attack between the ages of 30 and 40; the four who were markedly improved had had asthma for 1, 2, 3 and 14 years, whereas the other six patients who were relieved had had asthma for 1, 1, 2, 9, 10 and 30 years, respectively. Only two patients in this group began to have asthma after 40; one who had the onset at 42, with a duration of 3 years, was relieved, whereas the other who began to have asthma at 52, with a duration of one year, was markedly improved. Therefore, the age of onset had no bearing on the benefit from treatment, as many of those beginning to have asthma during adult life were relieved as of those who began to have asthma during childhood. Neither in these cases did the length of time which the patients had had asthma influence treatment; in fact, those who were relieved had had asthma for much longer periods than had those who were not relieved.

On comparing this group of sensitive cases with the sensitive ones presented in the preceding article it is noted that during childhood sensitization to the bacterial proteins corresponds relatively closely to those sensitive to other types of protein, but that during adult life sensitization to the bacterial proteins is relatively much more frequent than it was for other types of proteins. The duration of asthma among patients who were sensitive to the various types of proteins was relatively about the same and the percentage of cases being relieved was exactly the same for all proteins. The permanency of relief among those who were sensitive to and treated with bacteria is of much shorter duration than for those who were sensitive to and treated with animal hair proteins. With the bacterial cases relief continued for only a few months after treatment was stopped, and naturally this is all that would be expected for such a short course of treatment, together with the constant exposure to bacteria. Relief continues, however, as long as treatment is given, and in this way the bacterial cases resemble the food cases, since the food cases are free from asthma as long as those foods to which the patient is sensitive are omitted from the diet.

Nonsensitive patients treated with plain agar organisms.—Seventy-five patients were treated with vaccines made from the bacteria which were recovered from the patient's thick sputum when the sputum was streaked on large surfaces of plain agar. The various types of organisms were identified after twenty-four hours' growth, and the pre-

dominating organism was usually made into a vaccine and given to the patient, although in some instances a stock vaccine of that particular type of organism was given instead of the autogenous vaccine, and in a few instances a combination of sputum organisms was given. Thirty-five, or 46.6 per cent., of these patients were relieved of asthma, twelve others, or 16 per cent., were greatly improved, and twenty-eight, or 37.3 per cent., were not benefited.

The types of organisms recovered from the sputum and incorporated into vaccines in these 74 patients were as follows. Of the 35 patients who were relieved of asthma, in 8 cases the vaccine comprised *S. pyogenes aureus* alone, in one case a mixture of *S. pyogenes aureus* and *albus*, in one case a mixture of *S. pyogenes aureus* and a gram-negative staining bacillus,⁶ in one case a mixture of *S. pyogenes aureus* and a diphtheroid organism, in one case *S. pyogenes albus* alone, in 17 cases a diphtheroid organism alone, in 3 cases a gram-negative staining bacillus⁶ alone, in one case Friedländer's bacillus alone, and in the remaining 2 cases the organism was not identified. One of the foregoing patients who was relieved by diphtheroid vaccine also had Friedländer's bacillus in large numbers, but vaccines of this organism did not improve the patient, and another of the foregoing patients who was relieved by diphtheroid vaccine was not benefited by *S. pyogenes aureus* which was also present in the sputum in large numbers; therefore, these instances show the specificity of bacteria in the treatment of asthma. Of the 12 patients who were markedly improved, 7 were treated with diphtheroid vaccines alone, 2 with a mixture of *S. pyogenes aureus* and diphtheroid, 2 with *S. pyogenes aureus* alone and 1 with the gram-negative staining bacillus. One of those who was markedly improved by diphtheroid vaccine was not benefited by *S. pyogenes aureus* vaccine, and another who was markedly improved by diphtheroid vaccine was not benefited by the gram-negative staining bacillus, thus again showing the specificity of bacteria in the treatment of asthma. The 28 patients who were not benefited were given vaccines as follows: 8 were given *S. pyogenes aureus* alone, one *S. pyogenes aureus* alone and later *S. pyogenes albus* alone, 4 were given *S. pyogenes aureus* alone and later diphtheroid alone, one a combination of *S. pyogenes albus* and diphtheroid, one *S. pyogenes albus* alone, and the remaining 13 cases were given vaccines of diphtheroid organisms alone. A summary of the results from the use of vaccines made from the several types of predominating organisms in the sputum when grown on plain agar was as follows: diphtheroid alone,

6. This gram-negative staining bacillus, which will be frequently mentioned, was more or less motile, sometimes only sluggishly motile, at other times very actively motile; in the litmus-sugar-serum waters it reacted like the colon type of bacillus although it did not produce indol in Dunham's peptone solution.

17 relieved, 7 improved and 13 not benefited; *S. pyogenes aureus* alone, 8 relieved, 2 improved and 8 not benefited; *S. pyogenes albus* alone, 1 relieved and 1 not benefited; gram-negative staining bacillus, 3 relieved, 1 improved and 1 not benefited; Friedländer's bacillus, 1 relieved and 1 not benefited; since the remaining patients received a combination of bacteria in the vaccines, results cannot be attributed to any special type of organism.

The relationship between the age of onset of asthma and the results from vaccine treatment in this series of cases follows: Of those who began to have asthma between the ages of 1 and 5 years, 12 were relieved, 1 was improved and 2 were not benefited; of those whose onset of asthma began between the ages of 5 and 10 years, 5 were relieved and 2 were not benefited; of those whose onset began between the ages of 10 and 20, 3 were relieved, 1 was improved and 3 were not benefited; onset between 20 and 30, 3 were relieved, 7 were improved and 3 were not benefited; onset between 30 and 40, 9 were relieved, 3 were improved and 7 were not benefited; onset between 40 and 50, 2 were relieved and 7 were not benefited; onset above 50, none was relieved, 8 were improved and 4 were not benefited. It is evident that three-fourths of those who began to have asthma in childhood (from 1 to 10 years) were relieved; that half of those whose onset was between the ages of 10 and 40 were relieved; that a third of those whose onset was between 40 and 50 were relieved, and that after 50 none was relieved. Therefore, in general, the younger the patient is when asthma begins the better the prognosis, and in children the prognosis is very good.

Before we prognosticate, however, we must see what effect the duration of asthma may have on the results of treatment. Of those who had had asthma for one year, 3 were relieved, 2 improved and 4 not benefited; duration for two years, none relieved, 2 improved and 3 not benefited; three years' duration, 4 relieved, 2 improved and 4 not benefited; duration four years, 3 relieved, 1 improved and 1 not benefited; five years' duration, 2 relieved and no failures; six years' duration, 3 relieved and 1 not benefited; seven years' duration, 1 relieved and 2 not benefited; eight and nine years' duration, 1 each relieved and no failures; ten, twelve and fourteen years' duration, 2, 2 and 3, respectively, relieved and 1, 2 and 2, respectively, not benefited; sixteen years' duration, 2 relieved and 3 not benefited; twenty to thirty years' duration, 8 relieved and 5 not benefited. In other words, of those whose duration was from 1 to 5 years, 12 were relieved and 12 were not benefited; duration from 5 to 10 years, 8 were relieved and 4 were not benefited; duration from 10 to 20 years, 7 were relieved and 9 were not benefited; duration from 20 to 30 years, 8 relieved and

3 not benefited. Therefore, in these cases the length of time that a patient has had asthma makes little difference in the prognosis, and the duration in years of those relieved so closely parallels the duration of those not benefited that the latter serve as a good negative control for the positive results in the former.

From what has been shown in these cases it is evident that the best prognosis concerns those patients who begin to have asthma early in life and have not yet reached the age of 40 when treatment is begun, and that the worst prognosis concerns those patients who begin to have asthma late in life no matter for how short a time they have had it. In other words, the age of the patient when treatment is begun is an important fact, and the older the patient when treatment is begun the worse the prognosis. This is naturally what one would expect, because the older the patient the more liable is he to be in poor physical condition, and the poorer the patient's condition the less able is he to manufacture antibodies. Vaccines of course stimulate the production of antibodies and therefore they fail if the patient is unable to respond to their stimulus. The duration of relief from asthma in these cases also depends on the patient's ability to manufacture antibodies, and in this sense we mean resistance to disease. Some patients will remain free from asthma for months after treatment is discontinued, whereas others require the constant use of vaccines in order to be free, and when vaccines are stopped the condition quickly returns. Patients who have paroxysmal attacks of asthma, no matter how short the interval of freedom between attacks, are much easier to relieve of asthma than are those patients who have continuous asthma with no free intervals. Here again the principle of resistance enters and the fact that a patient has at times freedom from asthma means that he does have more or less resistance to the bacteria causing the trouble, and the fact that some patients have continuous asthma means that those patients never develop enough antibodies or resistance to at times temporarily recover from asthma. Therefore the prognosis in the nonsensitive asthmatic patient depends equally on the patient's resistance and on the selection of the proper vaccine for treatment.

Nonsensitive patients treated with organisms grown in dextrose bouillon.—This group of cases includes only those patients whose sputum when inoculated into dextrose bouillon grew types of organisms which resembled a streptococcus morphologically, and which, in addition, were gram-positive staining and bile insoluble. Therefore, in these cases the predominating organism when the sputum was grown in dextrose bouillon was probably a streptococcus, although no attempt was made in these instances to identify the particular type of

streptococcus, and vaccines were made directly from the dextrose bouillon culture after from twenty to twenty-four hours' growth by centrifugalizing out the bacteria, washing in normal saline and then suspending the washed bacteria in normal saline.

A total of twenty-four patients were treated with vaccines made in this manner. Nine, or 37.5 per cent., were relieved of asthma; six, or 25 per cent., were markedly improved, and nine, or 37.5 per cent., were not benefited at all.

The preceding groups of cases were discussed in considerable detail in regard to the age of onset and duration of asthma. This last group of cases is so small in number that much space and time may be saved by the use of a table from which general conclusions may be drawn at a glance (Table 1).

TABLE 1.—RESULTS OF TREATMENT OF NONSENSITIVE PATIENTS WITH DEXTROSE BOUILLON CULTURES

Relieved of Asthma			Markedly Improved			Not Benefited		
Number of Patients	Age of Onset, Years	Duration of Asthma, Years	Number of Patients	Age of Onset, Years	Duration of Asthma, Years	Number of Patients	Age of Onset, Years	Duration of Asthma, Years
1	1	20	1	1	25	1	4	60
1	3	2				1	8	21
1	5	1	1	5	26	1	21	12
1	7	30				1	26	18
1	10	16				1	28	18
1	35	1	1	32	5	1	30	20
1	40	4	1	32	10	1	36	3
1	41	1	1	42	5	1	37	2
1	39	20	1	37	15	1	40	2
9 or 37.5%			6 or 25%			9 or 37.5%		

Although the relationship in this group of cases as regards the age of onset and the duration of asthma between those who were relieved, improved and not benefited is too close to warrant definite conclusions, still the evidence is in favor of what the previous group of cases conclusively showed. Namely, that the younger the patient is when asthma began, irrespective of the duration, the better the prognosis, and that the older the patient is when asthma begins, no matter how short a time he has had asthma, the poorer the prognosis. The permanency of relief in the patients treated with streptococcus vaccines does not seem to differ from that in those treated as previously outlined in this paper.

Nonsensitive patients treated with several different vaccines.—The patients in this group were not only treated with the predominating

organism in their sputum when it was grown on plain agar and in dextrose bouillon, but also, if the patient was not relieved by such vaccines, other types of organisms were employed. In other words, different types of vaccines were tried, each one for a period of several weeks, until the proper one was found and relief or marked improvement resulted. Since, as already shown in this paper, of the organisms which were recovered from plain agar, the diphtheroid and *S. pyogenes aureus* usually predominated and were found to give relief most frequently, and of the organisms which were recovered from dextrose bouillon, the streptococci usually predominated and were found to give relief most frequently, these were the first to be tried and consequently they were used in most instances. When these failed, other organisms were used, so that in the cases which were not relieved at all, many different types of vaccines were employed. This method of treatment in these cases does not show the relative merits of growing bacteria for vaccines on any special kind of mediums, but it does show clearly the specificity of bacteria in the treatment of bronchial asthma.

Thirty-five patients were treated as outlined in the foregoing. Eleven, or 31.4 per cent., were relieved; 8, or 23 per cent., were markedly improved, and 16, or 45.6 per cent., were not benefited at all.

Of the eleven patients who were relieved, one was relieved by diphtheroid vaccines after streptococci had failed, one was relieved by a mixture of *S. pyogenes aureus* and *albus* after streptococci had failed; four were relieved by streptococci after diphtheroid vaccines had failed, and in one of these *S. pyogenes aureus* had also failed; the remaining five patients were relieved by *S. hemolysans* vaccines after diphtheroid vaccines had failed, and in three of these *S. pyogenes aureus* vaccine had also failed.

Of the eight patients who were markedly improved, two were markedly improved by diphtheroid vaccines after streptococci and *S. pyogenes aureus* vaccines had failed; one was markedly improved by streptococcus vaccines after diphtheroid vaccines had failed, and the remaining five patients were markedly improved by *S. hemolysans* vaccines after diphtheroid vaccines had failed, and in three of these *S. pyogenes aureus* vaccines and in another *S. albus* vaccine had also failed.

The sixteen patients who were not benefited were treated with the following types of vaccines: 13 with diphtheroids, 12 with streptococci, 4 with *S. hemolysans*, 7 with *S. pyogenes aureus*, 3 with *S. pyogenes albus*, 2 with gram-negative staining bacillus, and 1 with *B. pyocyaneus*, which happened to be present in the sputum in pure culture.

Therefore, in this group of cases the treatment of the patients who were relieved and who were markedly improved shows the specificity of bacteria in the treatment of bronchial asthma in that only one of many kinds of vaccines gave good results. The failure in treatment in the sixteen cases, although a wide range of bacteria were used in the vaccines, shows that nonspecific vaccine treatment is not beneficial in bronchial asthma.

Table 2 gives the age of onset and the duration of asthma in the thirty-five patients who were treated with many types of vaccines:

TABLE 2.—RESULTS OF TREATMENT WITH VARIOUS TYPES OF VACCINES

Relieved of Asthma			Markedly Improved			Not Benefited		
Number of Patients	Age of Onset, Years	Duration of Asthma, Years	Number of Patients	Age of Onset, Years	Duration of Asthma, Years	Number of Patients	Age of Onset, Years	Duration of Asthma, Years
1	1	11				1	5	25
1	2	4				1	6	9
1	7	2	1	6	37	1	6	55
1	8	13	1	8	30	1	7	9
1	13	37	1	10	40	1	16	4
1	18	20				1	16	15
1	19	24				1	31	4
1	20	22	1	21	8	1	34	2
1	24	14	1	35	3	1	35	3
1	26	1	1	36	2	1	35	13
1	34	5	1	50	5	1	35	17
			1	55	9	1	36	6
						1	40	6
						1	57	2
						1	60	1

In Table 2 it is noted that although the duration of asthma in the cases not benefited averages considerably less than the duration in the relieved cases, the age of onset of asthma, and consequently the age of the patient when treated, averaged much greater in the not benefited patients than in the relieved cases. Therefore, the large percentage of failures in the vaccine treatment in this group of cases, in spite of the fact that a wide range of vaccines including the predominating organism as well as others were used, was probably due to the more advanced age of the patient both when asthma began and when treatment was instigated.

Nonsensitive summer asthmatics treated with vaccines.—Since it is generally believed that the type of asthma which is limited to the

summer months is caused by pollens, it seems advisable to discuss briefly the following sixteen patients who were not sensitive to pollens although their attacks of asthma closely paralleled the pollination of plants. Of five patients who had had asthma all summer for five or more summers, with no asthma at other times of the year, and who would be considered sensitive to both the early and the late pollens, although they were not sensitive at all to pollens, two were relieved of asthma by vaccines of streptococci which predominated in their sputum when cultured in dextrose bouillon. One of these patients was not benefited by vaccines made from growing the sputum on plain agar, although she was relieved for two successive summers by streptococcus vaccines. A third patient was relieved by vaccines of *S. pyogenes albus* for two successive summers; this organism was used in the vaccine because it was present in the patient's nasal secretion in pure culture, and his nasal secretion was troublesome. The other two patients were not benefited by vaccines consisting of *S. pyogenes aureus*, *S. pyogenes albus* or diphtheroids. Two patients who had asthma only during June and July, the early pollen season, were not sensitive to pollens. One patient was relieved by vaccines of *S. pyogenes aureus* and the other patient was relieved for two successive summers by vaccines of *S. pyogenes albus*; the latter patient had had asthma for sixteen successive seasons. Three patients who had asthma only during July and August were not treated, because of the short duration of their attacks, and, furthermore, these untreated patients served as controls for the treated patients. Five patients had asthma during June, July and August. One patient was improved one summer by diphtheroid vaccines and was relieved the next summer by streptococcus vaccines; another patient was markedly improved by streptococcus vaccines; another patient was not benefited one summer by vaccines made from growing the sputum on plain agar, but was markedly improved the next summer by *S. hemolysans* vaccine; another patient was somewhat benefited one year by plain agar vaccines and another year by dextrose bouillon vaccines, but neither type of vaccines gave marked relief; the fifth patient was not benefited at all by streptococcus vaccine. Therefore, of sixteen non-sensitive summer asthmatics who were given vaccines, five were relieved of asthma, four were markedly improved, four were not benefited and three were not treated.

The following comparisons as regards treatment may be made between sensitive and nonsensitive asthmatic patients. In the previous article, which concerned patients sensitive to proteins, and in the first part of this article which concerns patients sensitive to bacterial proteins, it was shown that in general a favorable prognosis could be

anticipated irrespective of the age of onset of asthma or the age of the patient when treated. With the nonsensitive patients, however, the later the age of onset and the later the age of the patient when treatment is begun, the more unfavorable the prognosis. The duration of asthma alone played little part in the prognosis in either type of case. Seventy-five per cent. of the sensitive patients were relieved of asthma by treatment with the proteins to which they were sensitive, whereas only 40 per cent. of the nonsensitive patients were relieved of asthma by treatment with vaccines. The permanency of relief from asthma in the sensitive patients was of much longer duration than in the nonsensitive patients. Both the sensitive and the nonsensitive patients illustrate specificity in the treatment of bronchial asthma; that is, the specificity of proteins in the treatment of sensitive cases and the specificity of bacteria in the treatment of nonsensitive cases. We have, however, only inferred that nonsensitive asthmatic patients are not benefited by treatment with proteins. Because of the more or less general belief that infections may be alleviated by non-specific protein therapy—and in the case of chronic arthritis this is frequently found to be true—it seems worth while to mention our results in the treatment of the infectious or nonsensitive type of bronchial asthma with proteins.

Many of the nonsensitive or infectious type of asthmatics have been treated with various proteins. Three patients who were in the hospital wards because they were having severe asthma every day were given, intravenously, typhoid vaccine without improvement in the asthmatic symptoms. A week later a larger dose was given without any benefit. After this the patients were given, subcutaneously, two hundred million autogenous streptococcus vaccine made from growing their sputum in dextrose bouillon. A few days later one patient was somewhat improved, another seemed a little better and the third was not improved. A week later still the autogenous vaccine was increased to 250 million and a few days after this one patient was very much better, another was considerably improved and the third was somewhat better. The autogenous vaccine was given each week with gradual improvement in each instance until two patients left the hospital three weeks later and the third patient was able to leave in five weeks. Therefore, the intravenous typhoid vaccine was followed by no benefit, whereas the autogenous streptococcus vaccine was followed by a gradual though distinct improvement. Several of the nonsensitive summer asthmatics and some of the other non-sensitive cases were given courses of treatment with various pollens without benefit. A few nonsensitive patients were given wheat proteins and a few were given large doses of peptone subcutaneously without benefit. This

latter method of treatment is dangerous unless the patient is tested with peptone to rule out the possibility of his being sensitive to it. We feel that this fad of injecting patients with proteins to which they are not already sensitive is, in general, apt to be a mistake; the possibility of sensitizing patients to proteins, exclusive of typhoid vaccine, seems to outweigh the chance of improvement by such treatment.

In this work we have made our vaccines in different ways in the hope of making them more efficient. At first toluol was used as a preservative, but because of frequent, small, sore indurations at the site of inoculation, toluol was given up and 0.25 per cent. phenol was substituted; the phenol has been very satisfactory. For a long time we killed our vaccine by heating at 56 C. for two hours; lately, however, we have heated it at 56 C. for only three quarters of an hour and we are inclined to think better results follow the shorter heating. A leukocytic extract was also given with the vaccines without any beneficial effect; we have not given sensitized vaccine. Patients react differently to different amounts of vaccine; some patients will improve on small gradually increased amounts, whereas other patients do not improve until large amounts are given. Therefore, we now make two dilutions of each vaccine, one containing 1,000 million to the cubic centimeter, and the other containing 10,000 million to the cubic centimeter. The weaker vaccine is given first for several doses in rapidly increasing amounts in order to see how the patient reacts, and if neither beneficial nor unfavorable results follow, then the stronger vaccine is used, but if desirable results follow the weaker vaccine this is then given in gradually increased amounts at weekly intervals; the first dose is usually about 200 million. In the treatment of bronchial asthma we have given 3,700 doses of vaccine; that is to say, we have taken the trouble actually to count this number of injections and we do not know how many more we have given which we have not attempted to count. In only one instance did a really bad reaction result; that one patient had fever, general malaise and was in bed for two weeks; the vaccine proved to be sterile and the patient had no local reaction, therefore the patient was considered too susceptible for further treatment. Of the 3,700 doses of vaccine given, 800 were *S. pyogenes aureus*, 1,200 diphtheroids, 1,000 streptococcus and the remaining were miscellaneous vaccines.

CONCLUSIONS

Twenty-eight patients with bronchial asthma were treated with vaccines of the bacteria to which they were sensitive; 75 per cent. were relieved of asthma and 21 per cent. were improved.

Seventy-five nonsensitive patients were treated with vaccines made from culturing their sputum on plain agar; the predominating organism was usually the one selected for treatment; 46.6 per cent. were relieved of asthma and 16 per cent. were improved.

Twenty-four nonsensitive patients were treated with vaccines made from culturing their sputum in dextrose bouillon and using only the streptococci; 37.5 per cent. were relieved of asthma and 25 per cent. were improved.

Thirty-five nonsensitive patients were treated with vaccines made from culturing the sputum both ways; in other words, many types of vaccines were used; 31.4 per cent. were relieved and 23 per cent. were improved.

Sixteen nonsensitive summer asthmatics were treated with vaccines; 31.2 per cent. were relieved and 25 per cent. were improved.

Therefore, of 150 nonsensitive asthmatics who were treated with vaccines 40 per cent. were relieved and 20 per cent. were improved; these results should be compared with the treatment of sensitive patients as reported in the previous article, 75 per cent. of whom were relieved, and in this article 75 per cent. of whom were relieved.

With the sensitive cases, the age of onset of asthma, the duration of asthma and the age of the patient when treated had little to do with the prognosis; however, with the nonsensitive cases these facts had much bearing on the prognosis; the older the patient is when asthma begins and the older he is when treatment is begun, the more unfavorable the prognosis from vaccines in nonsensitive cases.

The permanency of relief from vaccines in the nonsensitive cases depends on the individual's resistance to the bacteria in question; therefore, the duration of relief from asthma varies. Some patients continue free from asthma after vaccines are discontinued for many months, others for only a month or two, and some patients require the constant use of vaccines to be free from asthma. Succeeding courses of vaccine treatment, provided that there has been no change in the bacteria which are causing the relapse, seem to relieve more promptly than the first course of vaccine treatment; when a relapse is not relieved by a second course of vaccines which previously did relieve, other bacteria should be suspected as the cause of asthma and new vaccines should be made.

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DIFFERENTIATION OF NEPHROPATHIES, CARDIOPATHIES AND ALLIED CONDITIONS BY THE DETERMINATION OF PHYSICAL CONSTANTS *

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As a means of differentiating nephropathies, cardiopathies, arteriosclerosis and essential hypertension, Butterfield, Erdwurm and Braddock¹ have employed certain physical methods of examining the blood serum, and they claim that each of these conditions is accompanied by characteristic changes that are of diagnostic value. During the two years which have elapsed since the publication of their paper, however, this method of examination has received little attention from clinical laboratories and workers. In order to secure data on the value of the method, we have applied it to a large number of serums, and the results of the investigation are incorporated in the present communication.

The following determinations were made: Refractive index, freezing point, specific gravity, total solids, inorganic salts (ash).

Method of Obtaining Serum.—Blood was drawn between 10 and 12 a. m., the patient having had nothing but a hospital breakfast. It was allowed to clot. Serum was drawn off and centrifuged the same day between 4 and 5 p. m. It was kept in the ice box overnight and the determinations were made the next day.

Methods.—The *refractive index* was determined with the Abbé refractometer. It is expressed as $(\Delta Nd \times 10^3)$ and represents the difference between the refractive indexes of serum and the index of water at the same temperature, 25 C., multiplied by 1,000.

The *specific gravity* was determined with the aid of a small (5 c.c.) flask provided with a ground glass stopper having a capillary bore. The weights of both the freshly boiled, distilled water and the serum were obtained in the same way. The flask was filled with the liquid at about 20 C., stoppered, and the excess forced out through the capillary bore. The flask and contents were allowed to warm up slowly to 25 C., then wiped clean with filter paper to remove any of the overflow which may have adhered to the outside, and carefully weighed. From this weight was subtracted the weight of the empty flask. The result gave the weight of the serum in one case and the weight of the same volume of water in the other. Dividing the weight of the serum by that of the water gives the specific gravity.

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1. Butterfield, Erdwurm and Braddock: Am. Jour. Med. Sc., 1916, 151, No. 63.

The *freezing point* was determined with the Beckmann apparatus in the usual manner. The determinations were made in duplicate. When discrepancies occurred, the determination was repeated three or four times until the right value was obtained. The values represent the fraction of a degree below zero at which the serum freezes.

Total solids were determined in the usual manner by drying to constant weight at a temperature of 90 to 95 C.

Ash was determined by drying, then by ashing at a low red heat so as to avoid the volatilization of the chlorids. The crucibles used were small, weighing between 6 and 8 gm., thus minimizing the effect of "dead" weight.

TABLE 1.—NORMALS

Case No.	Age	Sex	Refractive Index	Specific Gravity	Freezing Point	Solids, per Cent.	Ash. per Cent.
106	26	♂	15.0	1.0263	0.609	8.4	0.75
71	25	♂	15.7	8.8	0.76
72	24	♀	15.7	1.0286	0.613	9.2	0.75
N1	26	♂	15.8	1.0258	0.568		
N2	50	♀	16.2	1.0284	0.562		
N3	45	♀	16.3	1.0283	0.550		
N4	17	♂	16.4	1.0295	0.570		
N5	21	♂	16.5	1.0265	0.570		
104	25	♂	16.5	1.0277	9.4	0.80
N6	45	♂	16.0	1.0295	0.605		
N7	22	♂	16.8	1.0278	0.570		
N8	21	♂	16.9	1.0275	0.576		
107	27	♀	17.0	1.0284	0.595	9.7	0.76
N9	23	♂	17.3	1.0278	0.558		
N10	21	♂	17.4	1.0278	0.567		
N11	20	♂	17.5	1.0292	0.557		
N12	25	♂	17.5	1.0280	0.564		
105	25	♂	17.5	1.0297	0.620	9.9	0.76
N13	20	♂	17.6	1.0297	0.561		
N14	20	♂	17.8	1.0292	0.575		
N15	20	♂	18.0	1.0294	0.595		
N16	28	♂	18.2	1.0298	0.565		
N17	39	♂	18.4	1.0301	0.577		

Grouping of Cases.—It is difficult to find pure cases, that is cases having only one affliction. Therefore, we grouped them according to the most prominent and apparently primary lesion. Whenever the secondary lesion was at all prominent and when it was suspected of modifying the constants due to the primary, it was noted. This was done to throw light on those cases that seemed out of place in the group assigned them by the diagnosis of the attending physicians.

The accompanying tables show the results obtained. The urine picture, the blood pressure and the degree of nitrogenous retention are also given.

TABLE 2.—CHRONIC NEPHRITIS WITH EDEMA

Case No.	Age	Sex	Urine	Blood Pressure	Nitrogen Retention	Condition	Specific Gravity	Refractive Index	Freezing Point	Solids, per Cent.	Ash, per Cent.
27	35	♂	Alb. ++++; many casts	165/100	Slight	Unimproved	1.0198	10.3	0.662	6.1	0.74
26	14	♀	Alb. 7%; many casts	150/100	Slight	Improved	1.0179	10.5	0.761	5.9	0.73
1	14	♀	Alb. 7%; many casts	150/100	Slight	Improved	1.0179	10.5	0.616	5.5	
69	14	♀	Alb. 7%; many casts	150/100	Slight	Improved	1.0180	11.0	0.625	6.5	0.76
25	57	♂	Alb. +; few casts; Exer. 50%	180/92	Slight	Improved	1.0217	11.9	0.672	7.1	0.75
15	42	♂	Alb. ++++; many casts; Exer. 16%	196/99	Slight	Improved	1.0218	12.0	0.671	7.22	0.91
76	38	♂	Alb. +++; few casts; Exer. 3%	154/80	Moderate	Died	1.0223	12.5	0.652	7.2	0.83
35	25	♀	Alb. ++++; few casts	168/56	Moderate	Died	1.0201	12.5	7.6	0.87
86	40	♂	Alb. ft. tr.; no casts; Exer. 45%	150/80	Slight	Improved	1.0221	12.5	0.560		
90	..	♂	Improved	1.0224	12.5			
96	53	♀	Alb. +++; many casts	145/108	Moderate	Died	1.0236	12.5	0.640	7.3	
102	60	♂	Alb. +; few casts	195/120	None	Improved	1.0246	13.5	0.630	8.1	
23	67	♂	Alb. ++; few casts	195/90	Marked	Died	1.0243	13.5	0.939	7.7	0.75
74	63	♂	Alb. +++; few casts	240/130	Marked	Improved	1.0243	13.5	0.619	7.6	0.74
97	51	♂	Alb. +; no casts	170/100	Moderate	Unimproved	1.0246	13.5	0.650	6.8	
92	..	♂	Improved	1.0215	13.5	0.930	7.9	
46	38	♂	Alb. +; many casts; Exer. 55%	140/90	Slight	Improved	1.0248	13.7	0.620	7.8	0.68
64	56	♂	Alb. ++; occ. east; Exer. 10%	140/90	None	Died	14.4	0.654	8.3	0.74
50	34	♀	Alb. trace; many casts	268/156	Moderate	Improved	1.0251	15.3	0.630	8.7	0.80
49	39	♀	Alb. ++++; occ. east; Exer. 50%	185/90	None	Improved	1.0270	15.5	0.602	8.9	0.89
87	40	♂	Alb. +; no casts	176/98	None	Improved	1.0273	16.5	0.580	8.9	
84	34	♀	Alb. +++; many casts; Exer. 20%	190/140	Marked	Dead	1.0290	16.7	0.835	6.8	
81	46	♂	Exer. 8%	230/130	Marked	Dead	1.0290	17.5	0.658	9.9	0.73

Normal Values.—The refractive indexes range from 15.7 to 18.4; specific gravity 1.0258 to 1.030; freezing point lowering 0.550 degrees to 0.620 degrees; solids 8.4 per cent. to 9.9 per cent.; ash 0.75 per cent. to 0.80 per cent.

Chronic Nephritis with Edema.—The refraction, the specific gravity and the solids are very low. A few cases, however, show values well within the normal range. The freezing point lowering is greater than normal, and the ash is normal, pointing toward a dilution of the blood with fluid high in organic crystalloids and normal in inorganic salts.

TABLE 3.—CHRONIC NEPHRITIS WITH UREMIA

Case No.	Age	Sex	Urine	Blood Pressure	Nitrogen Retention	Condition	Specific Gravity	Refractive Index	Freezing Point	Solids, per Cent.	Ash, per Cent.
88	39	♂	Alb. ++++; many casts; Exer. 23%	240/145	Moderate	Improved	1.0234	13.0	0.590		
103	60	♂	Anuria	130/0	Marked	Died	1.0236	13.5	0.630	7.8	
108	26	♂	Alb. ++++; occ. cast	260/145	Marked	Slight improvement	1.0243	14.0	0.685	8.2	0.78
47	65	♂	Alb. ++++; few casts	Died	1.0254	14.7	0.700	8.3	0.73
85	53	♂	Alb. trace; few casts	230/120	Moderate	Died	1.0247	14.7	0.515	9.1	
109	27	♂	Alb. ++++; no casts; R.B.O. +++	240/140	Marked	Died	1.0273	15.5	0.665	8.7	0.65
48	45	♀	Alb. ++++; no casts; Exer. 1%	240/130	Marked	Died	1.0276	15.6	0.676	9.1	0.70
93	..	♀	Marked	Died	1.0264	17.5	0.685	9.1	

The specific gravity and the refraction vary inversely with the degree of edema. Beginning with Case 27 and going to Case 81, we pass from very marked edema to very slight edema, with isolated exceptions. Beginning with Case 102, we find added heart complications. These complications tend to raise the specific gravity and the refraction slightly, because cardiac patients with edema have somewhat higher values than nephritics with edema. From Case 50 and upward, in which the values are normal, we find hypertension in all the cases. This hypertension raises the values from subnormal to normal. In some of the lower cases, hypertension was present, but the edema was much more marked and its effect overshadowed that of the hypertension.

Chronic Nephritis with Uremia.—The refraction is lower than normal, but higher than in nephritis with edema. This is because the blood contains retention products which in themselves have refractive power, and, therefore, increase to a slight extent the refraction of the

otherwise diluted serum. The specific gravity and the total solids are somewhat lower than normal, but much higher than in edematous nephritics, because in uremia the blood is diluted with fluid of urinary composition, while in edema it is diluted primarily with isotonic salt solution. The lowering of the freezing point is usually greater than normal. This is also explained by urinary admixture; the urine having a greater lowering of the freezing point than the serum has. The ash is a little lower than normal, thus suggesting a retention of the organic crystalloids to a much greater extent than the inorganic salts, and, therefore, increasing the absolute but decreasing the relative values.

TABLE 4.—CHRONIC NEPHRITIS WITH EDEMA AND UREMIA

Case No.	Age	Sex	Urine	Blood Pressure	Nitrogen Retention	Condition	Specific Gravity	Refractive Index	Freezing Point	Solids, per Cent.	Ash, per Cent.
22	50	♂	Alb. ++++; many casts; Excr. 20%	240/110	Marked	Died	1.0214	11.4	0.983	6.72	0.74
60	60	♂	Few casts; Excr. 45%	190/100	None	Slight improvement	1.0224	12.9	0.821	7.1	0.70
32	67	♂	Alb. ++; few casts	195/90	Marked	Died	1.0261	14.5	0.713	8.4	0.77
4	23	♂	Alb. ++++; many casts	240/120	Marked	Died	1.0242	14.5	0.720		
3	23	♂	Alb. ++++; many casts	240/120	Marked	Died	1.0256	15.5	0.675		
100	62	♂	Alb. ++++; many casts; many R.B.O.	180/95	Marked	Died	1.0280	16.0	0.700	7.33	
5	23	♂	Alb. ++++; many casts	240/120	Marked	Died	1.0264	16.5	0.770		
13	50	♂	Alb. ++; many casts; Excr. 6%	210/160	Moderate	Unimproved	1.0273	15.5	0.687	9.11	0.89

Chronic Nephritis with Uremia and Edema.—In these cases the refraction is also very low, and the tendency is for a smaller percentage of cases to reach the low normal figures. This is due to greater retention than in either of the foregoing sets of cases, edema alone or uremia alone. If we were to determine the refraction due to the uremic substances, and deduct it from the refraction as usually reported, the resulting figures would fall very much below that found in edema alone. The specific gravity and the solids are low and each seems to be an average of the values found in edema and of that found in uremia. There are many cases, however, whose values run well into the normal figures. The freezing point depression, on the contrary, is always great, due to the fact that large amounts of salts are retained in the blood, and much water also is added due to the

edema. This water ionizes the salts to a much greater extent than in uremia alone, and hence the increased freezing point. This is a good point of differentiation between uremia alone, edema alone, and that of uremia plus edema. The former two have low refractive indexes and low specific gravity, with slightly raised freezing points; the latter have low refractive indexes and low specific gravity, with a marked rise in freezing point. Nothing worthy of note is shown by the ash determination.

In Cases 22 and 60, the edema was marked; in 22 uremia was marked; in 60 the uremia was much less. Case 32 had very slight edema. Numbers 3, 4 and 5 are the same case at different stages. The uremia increased until death. Case 13 is a picture of both marked uremia and edema.

TABLE 5.—CHRONIC NEPHRITIS WITHOUT EDEMA OR UREMIA

Case No.	Age	Sex	Urine	Blood Pressure	Nitrogen Retention	Condition	Specific Gravity	Refractive Index	Freezing Point	Solids, per Cent.	Ash, per Cent.
31	53	♂	Alb. +++; occ. cast	172/112	Improved	1.0241	13.5	0.709	7.9	0.73
91	30	♂	Alb. 30%; many casts; Excr. trace	180/140	Marked	Died	1.0254	13.8	0.645	10.2	
83	31	♂	Alb. +++; occ. cast	195/145	Moderate	Improved	1.0250	15.0	0.705	8.3	
73	45	♂	Alb. ++++; many casts	210/120	Marked	Unimproved	1.0273	15.6	0.641	9.2	0.80
67	45	♂	Alb. ++++; many casts	280/160	Marked	Unimproved	1.0290	16.5	0.706	9.3	0.76

Chronic Nephritis without Uremia and Edema.—The refraction is somewhat lower than the normal, but higher than that in edema, or that in uremia plus edema. This fact is a great aid in the diagnosis of the foregoing condition. The specific gravity is much the same as in uremia, that is to say, slightly lower than normal, but much higher than the beforementioned nephritic groups. The freezing point has values higher than normal; the solids and the ash are about the same as in normals. In this set of cases it is interesting to note that the specific gravity and the refraction are in no way related to the change in blood pressure.

Cardiac Decompensation with Edema.—In this set of cases all the values are similar to those in nephritis with edema, with the exception that the refraction, the specific gravity and the solids run just a trifle lower in nephritis. The lower these values are, the more marked the edema. With three exceptions, Cases 89 to 16 have nephritis as a secondary diagnosis. Might it not be possible that their edema is due

TABLE 6.—CARDIAC DECOMPENSATION WITH EDEMA

Case No.	Age	Sex	Urine	Blood Pressure	Nitrogen Retention	Condition	Specific Gravity	Refractive Index	Freezing Point	Solids, per Cent.	Ash, per Cent.
89	..	♂	Improved	1.0190	13.0	0.560	6.8	
56	67	♂	Alb. trace; occ. cast; Excr. 10%	200/80	Improved	1.0243	12.5	0.653	7.0	0.78
63	30	♂	Alb. +++; many casts	Died	1.0236	12.5	0.659	7.8	0.71
65	34	♂	Alb. ++++; many casts; Excr. 25%	175/100	Marked	Slight improvement	1.0226	12.5	0.727	7.1	0.75
78	57	♂	Alb. ++; many casts	Improved	1.0225	12.5	0.693	6.9	0.71
98	61	♂	Alb. ft. tr.; no casts	150/100	Slight	Improved	1.0100	12.7	0.596	7.4	
37	26	♀	Alb. ++; no casts	160/70	Died	1.0242	12.8	0.678	7.3	0.81
53	51	♂	Alb. ++; many casts	158/112	Moderate	Improved	1.0235	12.8	0.615	7.4	0.78
38	65	♂	Alb. v. f. tr. no casts; Excr. 35%	180/94	None	Improved	1.0223	13.0	0.672	7.2	0.74
79	65	♂	Alb. trace; occ. cast; Excr. 40%	138/78	Improved	1.0242	13.0	0.597	7.4	0.73
52	42	♀	Alb. +++; few casts	144/110	None	Died	1.0237	13.1	0.633	7.6	0.73
18	60	♂	Alb. trace; few casts	178/110	Slight	Died	1.0235	13.4	0.724	7.2	0.74
16	53	♂	Alb. +++; few casts; Excr. 37%	186/110	Slight	Improved	1.0239	13.5	0.679	7.7	0.67
29	33	♀	Alb. ++; few casts	215/160	Marked	Died	1.0252	13.5	0.816	8.0	0.77
39	41	♂	Alb. +++; no casts; Excr. 31%	170/117	Improved	1.0247	13.5	0.615	7.9	0.76
57	52	♂	Alb. trace; occ. cast; Excr. 13%	120/85	None	Improved	1.0248	13.5	0.920	7.7	0.74
68	49	♂	Alb. ++; occ. cast; Excr. 18%	152/78	None	Improved	1.0254	13.5	0.698	7.7	0.72
30	48	♂	Alb. trace; no casts; Excr. 26%	164/90	None	Improved	1.0250	14.3	0.691	8.0	0.71
44	34	♂	Alb. ++++; many casts; Excr. 25%	175/100	Marked	Slight improvement	1.0250	14.4	0.810	8.2	0.80
45	33	♂	Alb. +++; few casts; Excr. 70%	120/70	Moderate	Died	14.5	0.635	8.6	0.72
34	63	♂	Alb. +; no casts; Excr. 45%	165/120	Died	1.0258	15.4	8.4	0.76

TABLE 6.—CARDIAC DECOMPENSATION WITH EDEMA—(Continued)

Case No.	Age	Sex	Urine	Blood Pressure	Nitrogen Retention	Condition	Specific Gravity	Refractive Index	Freezing Point	Solids, per Cent.	Ash, per Cent.
17	64	♂	Alb. ++; no casts; Exer. 6%	138/100	Slight	Improved	1.0271	15.5	0.686	8.7	0.66
33	37	♂	220/140	Improved	1.0262	16.5	0.765	6.7	0.74
19	51	♂	Alb. ++++; many casts	135/100	Slight	Dead	1.0289	17.0	0.709	8.34	0.68
21	37	♂	Alb. ++; few casts	100/100	Slight	Dead	17.5	0.825	9.63	0.68
80	58	♂	Alb. trace; occ. cast; Exer. 25%	100/78	Slight	Dead	1.0312	19.4	0.623		
42	42	♂	120/80	Slight	Improved	1.0255	14.7	0.655	8.6	0.76
28	45	♀	Improved	1.0263	15.0	0.555	8.6	0.77

to that condition primarily? If these cases are put into the nephritic group, and those in the nephritic group with cardiac changes as their secondary lesion are put into the cardiac group, a distinct enough line is obtained, which separates the two groups. This grouping could be used in diagnosing cardiopathy and nephropathy. But taking the diagnosis of the clinicians as a basis, the two groups are intermixed.

TABLE 7.—ARTERIOSCLEROSIS

Case No.	Age	Sex	Urine	Blood Pressure	Nitrogen Retention	Condition	Specific Gravity	Refractive Index	Freezing Point	Solids, per Cent.	Ash, per Cent.
101	60	♂	Alb. ft.tr.; no casts	200/110	Improved	1.0238	13.4	0.620	8.1	
62	35	♂	228/136	Improved	1.0250	14.4	0.770	7.9	0.75
75	52	♂	Alb. ++; many casts; Exer. 6%	120/80	Moderate	Improved	1.0253	14.4	0.715	7.9	0.75
36	56	♂	Alb. ++; no casts	220/90	Slight	Improved	1.0262	14.8	0.897	8.4	0.76
61	50	♂	210/100	None	Improved	1.0270	15.4	0.640	8.5	0.75
12	47	♂	130/60	None	Improved	1.0327	16.0	0.603	9.1	0.82
54	40	♂	Alb. ++; few casts	180/120	None	Improved	1.0282	16.5	0.617	9.4	0.77
99	80	♂	Alb. trace; few casts	230/110	Slight	Improved	1.0280	17.0	0.740	9.3	
55	50	♂	Alb. ++++; few casts	250/150	Slight	Improved	1.0283	17.3	0.879	9.4	0.76
59	58	♂	180/82	Dead	1.0331	19.5	0.633	10.9	0.73

Arteriosclerosis.—In this group we have placed all cases diagnosed primarily as arteriosclerosis, regardless of the blood pressure.

The solids, the refraction and the specific gravity are not always higher than normal, as Butterfield and his co-workers found in their cases. Although some of these cases have much higher values than normals, there are just as many with a subnormal value. The freezing point and ash are the same as in normals.

Case 101 had as a secondary condition, nephritis and edema. Case 36 had cardiac decompensation as a secondary lesion. In these arteriosclerotic cases the values found in no way varied with the blood pressure.

TABLE 8.—ESSENTIAL HYPERTENSION

Case No.	Age	Sex	Urine	Blood Pressure	Nitrogen Retention	Condition	Specific Gravity	Refractive Index	Freezing Point	Solids per Cent.	Ash per Cent.
51	63	♂	Alb. v. f. tr.; no casts	235/130	Moderate	Improved	1.0281	16.5	0.725	9.3	0.89
20	44	♀	Alb. +++; few casts; Exer. 50%	270/170	None	Slight improvement	1.0288	17.5	0.670	9.7	0.70
82	47	♂	205/0	None	Improved	1.0292	18.0	0.691	9.7	0.74

Essential Hypertension.—The solids and especially the freezing point, are much higher than normal. The other values are unchanged. This class is very small, only three cases, because we included only those cases whose clinical picture was solely that of hypertension.

Summary, in Chart Form, of Work Done.—In order to bring out to the best advantage the findings in the tables, we have plotted all the results. As ordinates we have the percentage of cases, as abscissae the values of the constant named at the head of each chart. Thus by Chart 7, the lowest curve, that for normals, is meant that 4 per cent. of the total of 23 cases has a refraction of 15.5 or below, 34 per cent. has a refraction of 15.6 to 16.5, 38 per cent. has 16.6 to 17.5, and 22 per cent. has 17.6 to 18.5. The majority of normals, therefore (72 per cent.) have a refraction between 15.6 and 17.5. This form of representation shows vividly how the constants are shifted in the various conditions, and also how much they overlap. Thus, in chronic nephritis with edema, the majority of cases are shifted much to the left (lower values), but some overlap the normal. Wherever the curve does not pass through the points marked by crosses, it is because we always connected the last point with the highest point, for it may be possible that in another set of cases these points may be somewhat higher.

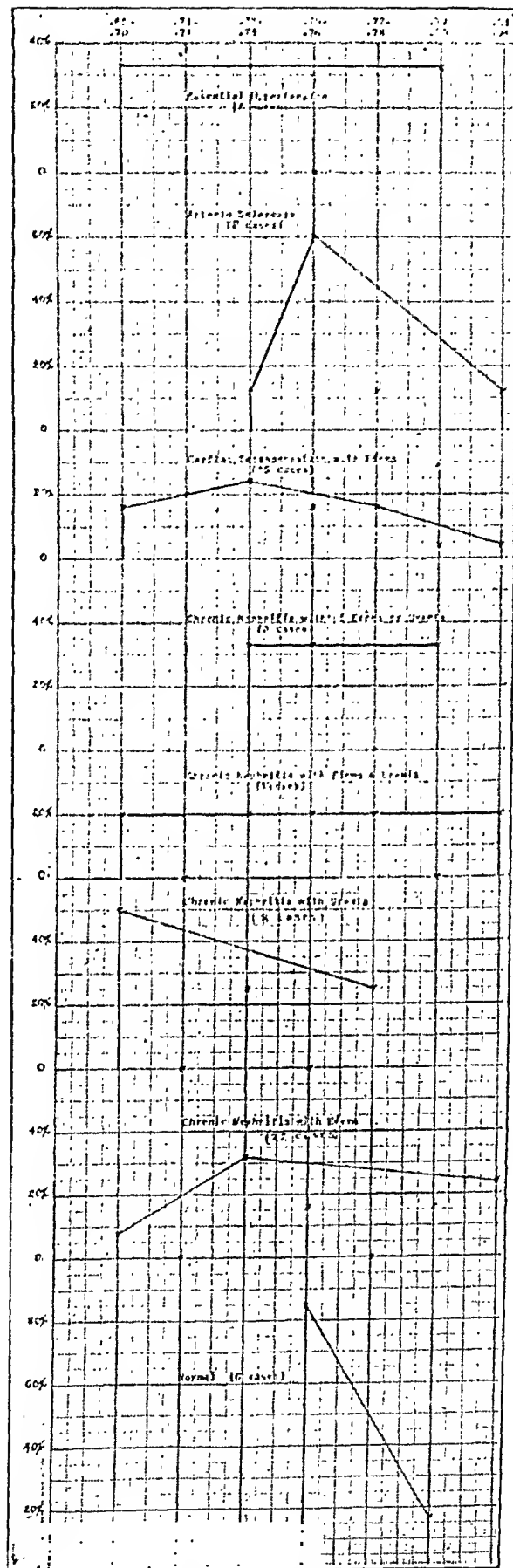


Chart 1.—Refractive index.

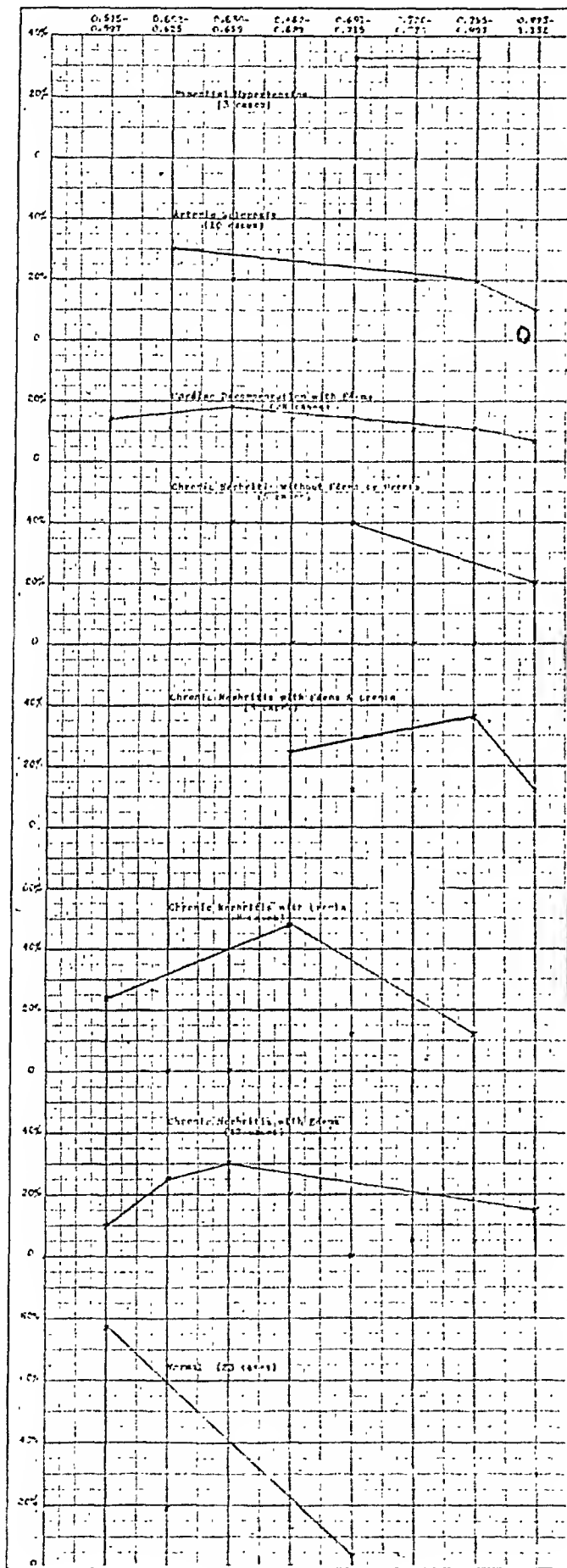


Chart 2.—Solids.

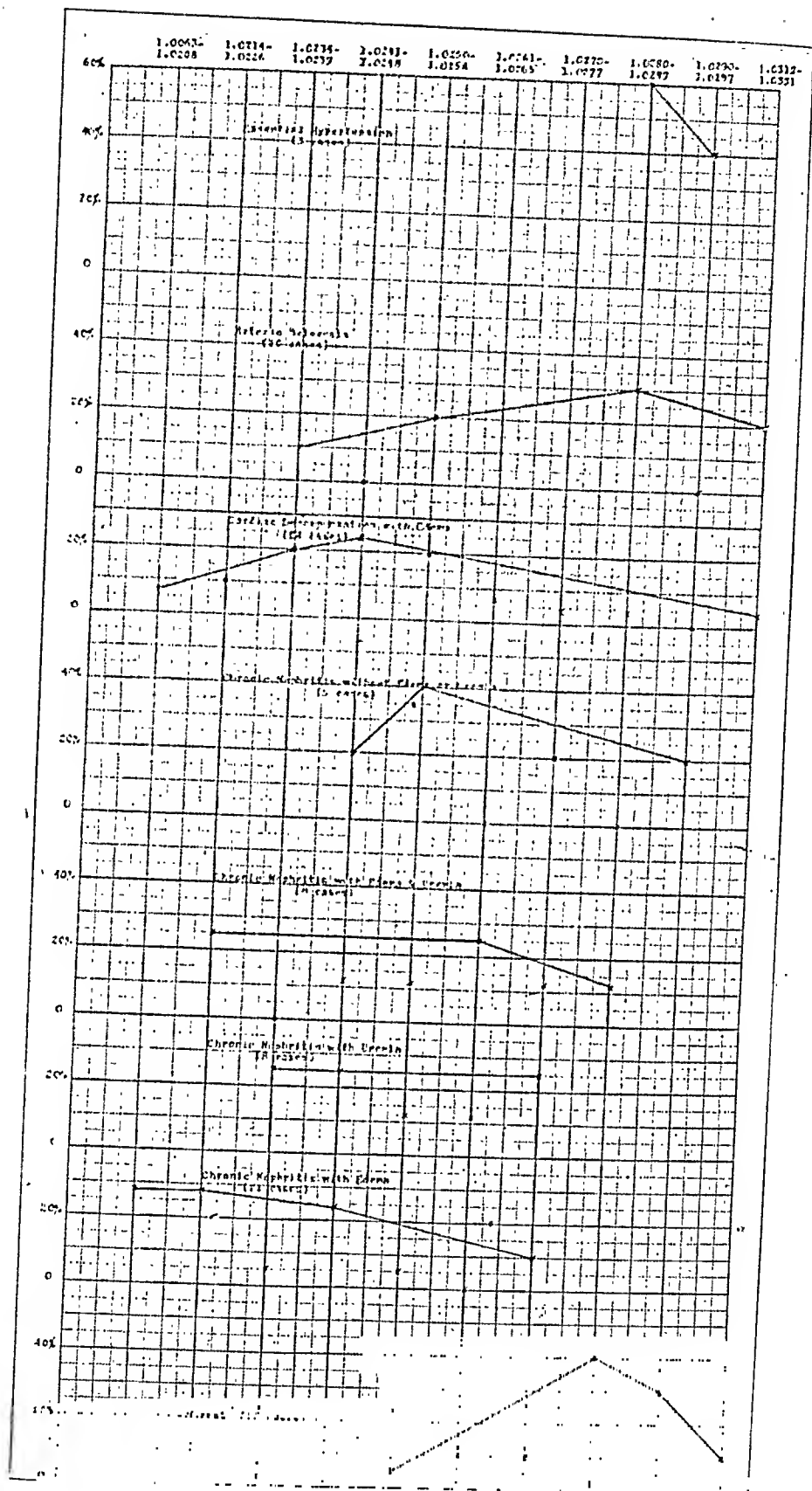


Chart 3.—Specific gravity.

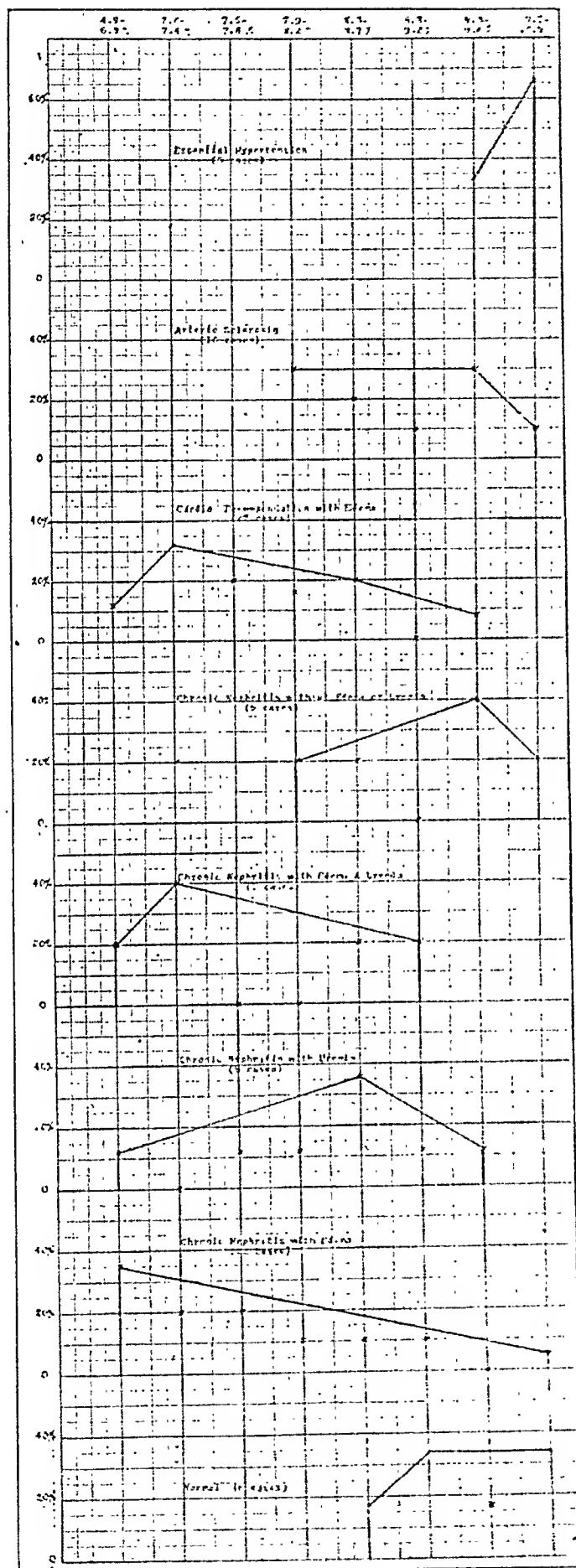


Chart 4.—Freezing point.

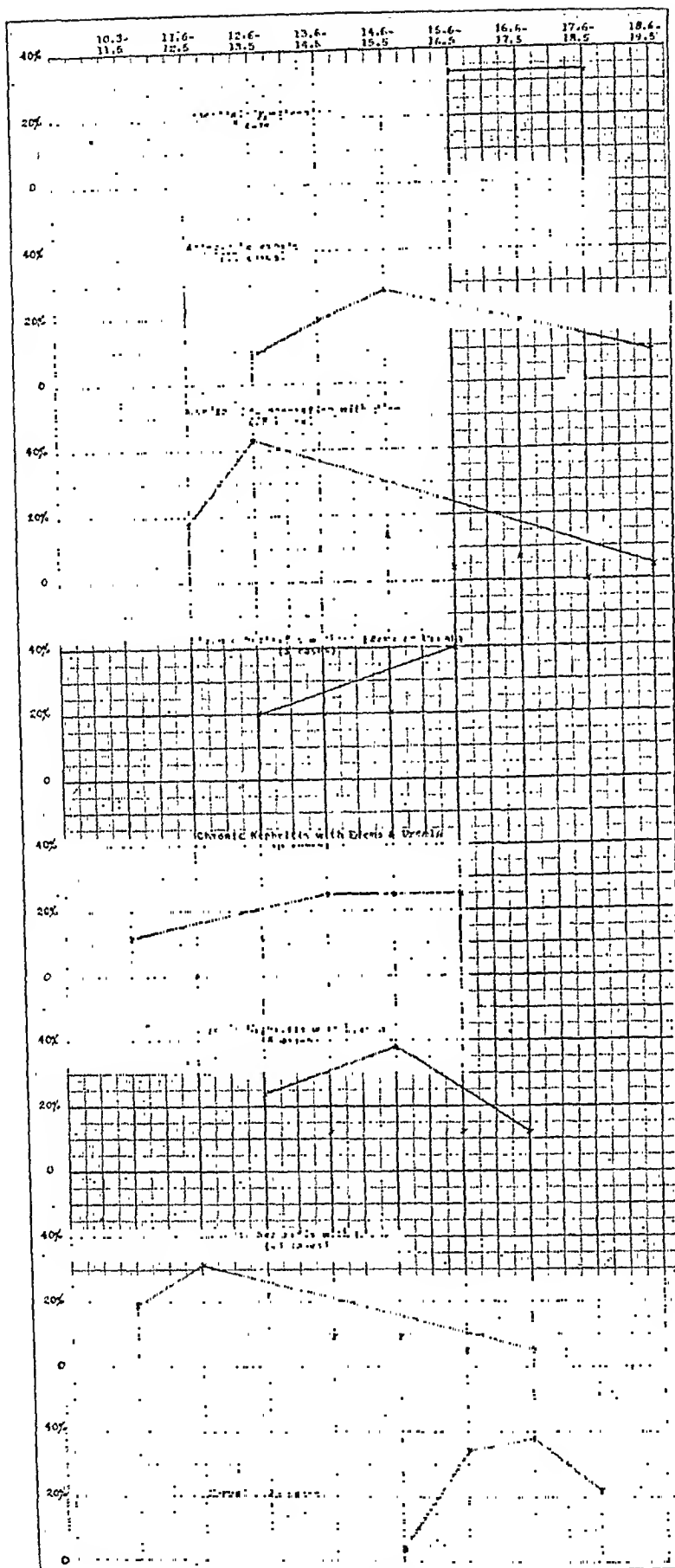


Chart 5.—Ash.

DISCUSSION OF CHARTS

Refraction.—All run lower than normals, except hypertension cases, which are the same as normals. Nephritis with edema is lowest; nephritis with uremia and edema run slightly lower than with uremia alone; nephritis without either uremic or edematous symptoms is a little lower than normal, but higher than the former two; arteriosclerosis is somewhat lower than normal (Chart 1).

Solids.—These run parallel with refraction. This is because the albumin and globulin account for the major portion of the solids (about 80 per cent.), except in nephritis with uremia and edema; here the refraction is more than that which corresponds to the solids. This is due perhaps to the increased uremic substances which affect increasingly the refraction.

A point of differentiation: Nephritis with edema has low solids and low refraction; nephritis with edema and uremia has low solids and higher refraction (Chart 2).

Specific Gravity.—This runs parallel with the preceding two (Chart 3).

Freezing Point.—All types of nephritics have a larger value than normal. Those with edema have values nearest the normal. The blood does not become as concentrated with crystalloids as the other types of nephritis. The cardiac and arteriosclerotic patients have a great range of values, and, therefore, they are of less significance. It is interesting to note that hypertension values are all normal except the freezing point, which is much lowered (Chart 4).

Ash.—Cardiac patients with edema have a lowered inorganic content; nephritic patients without edema, and cases of hypertension, are normal in this respect (Chart 5). Some nephritics with edema have lower ash content and some higher than normal. It is interesting to note that in nephritis with uremia the ash is lower than normal. This suggests that the organic crystalloids and not the inorganic increase in the blood.

SUMMARY

1. Serum values in normal individuals are given for refractive index, specific gravity, freezing point, solids and ash.

2. Determination of these constants, as well as the blood pressure, nitrogen retention and urine picture are reported in chart form in the following classes of cases: Chronic nephritis with edema, with uremia, with edema and uremia, without edema and uremia; cardiacs; arteriosclerosis, and cases of hypertension.

3. The values found in these various conditions overlap each other, and also overlap the normals to a large extent. They show no sharp division as do the cases cited by Butterfield, Erdwurm and Braddock.¹

4. Charts are inserted which may be of great aid in elucidating questionable cases before a practitioner.

5. Interesting points brought out are the following:

a. Edematous fluid not only collects in tissues, but also dilutes the blood in amount proportional to the edema.

b. Uremic blood is diluted with a fluid of urinary composition. The organic crystalloids seem to be retained to a greater extent than the inorganic salts.

c. In uremia plus edema, more fluid is retained in the blood than in either of the above two classes. This fluid differs from the edematous in being more concentrated with organic substances.

6. Serum pictures:

NEPHRITIS WITH EDEMA

Refraction	Very low
Specific gravity	Very low
Solids	Very low
Freezing point	Slightly high
Ash	Normal

NEPHRITIS WITH UREMIA

Refraction	Low
Specific gravity	Slightly low
Solids	Slightly low
Freezing point	Slightly high
Ash	Slightly low

NEPHRITIS WITH UREMIA AND EDEMA

Refraction	Low
Specific gravity	Low
Solids	Low
Freezing point	Very high
Ash	Not significant

NEPHRITIS WITHOUT UREMIA AND EDEMA

Refraction	Slightly low
Specific gravity	Slightly low
Solids	Normal
Freezing point	Slightly high
Ash	Normal

CARDIACS WITH EDEMA

Refraction	Very low
Specific gravity	Very low
Solids	Very low
Freezing point	Normal
Ash	Normal

ARTERIOSCLEROSIS

Refraction	Not significant
Specific gravity	Not significant
Solids	Not significant
Freezing point	Normal
Ash	Normal

HYPERTENSION

Refraction	Normal
Specific gravity	Normal
Solids	High
Freezing point	High
Ash	Normal

OBSERVATIONS CONCERNING THE PATHOLOGY OF PANCREATIC FERMENTS*

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INTRODUCTION

At present it is generally recognized that almost all enzymes seem to be toxic when introduced into animal bodies. The first thorough study of the toxicity of enzymes was made by Hildebrandt¹ in 1890. He found that pepsin, diastase, chymosin, emulsin, invertase and myrosin were all toxic; so much so that they produced trembling, uneasiness, difficulty in walking, dyspnea and rising temperature as symptoms. In addition there were numerous hemorrhages from serous and mucous membranes, the lungs, muscles, kidneys, intestines and brain; thrombosis in the body; interference with blood coagulation; fatty degeneration of the myocardium; fatty and parenchymatous degeneration of the liver and hyperemia and parenchymatous and fatty degeneration of the kidney as anatomic changes.

In 1899 Piquet² also observed that trypsin and pepsin increased the coagulability of the blood, but after such increase thrombosis frequently occurred.

Morgenroth³ found that injection of lab ferment subcutaneously caused an abscess at the site of injection. Achalme,⁴ in 1901, also observed that the sterilized pancreatic juice injected subcutaneously into guinea-pigs produced a local gelatinous edema followed by gangrene. In 1903, Lombroso⁵ found that an inactivated pancreatic juice was much less toxic than the activated.

Noguchi,⁶ in 1907, observed that pancreatic lipase is hemolytic when introduced into the blood. In 1911, Kirchheim⁷ found that the intravenous injections of pancreatic juice cause death, with lesions in the heart muscle and severe hemorrhage.

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1. Hildebrandt: *Virchows Arch. f. path. Anat.* **121**: 1890.

2. Piquet: *Arch. d. méd. exper.*, 1899, No. 11.

3. Morgenroth: *Centralbl. f. Bakteriöl.* **26**: 1899, Nos. 11 and 12.

4. Achalme: *Ann. de l'Inst. Pasteur* **15**: 1901, No. 10.

5. Lombroso: *Abstr. in Biochem. Centralbl.* **1**: 1903.

6. Noguchi: *Biochem. Ztschr.* **6**: 1907.

7. Kirchheim: *Arch. f. exper. Path. u. Pharmakol.* **66**: 1911.

Jobling, Petersen and Eggstein,⁸ in 1915, stated that the intravenous injection of trypsin in dogs results in shock similar in many respects to anaphylactic and peptone shock.

My own experiments on the pathology of pancreatin, especially on the toxicity of pancreatin introduced into the circulating blood stream of rabbits, in their results resemble in essential points as to physical symptoms Hildebrandt's observation on the toxicity of various enzymes.

A. TOXICITY OF PANCREATIN

Experiment 1.—For this experiment I employed fifty-three rabbits. Forty-four of these rabbits were injected with a 1 per cent. native pancreatin salt solution filtered through a Berkefeld filter, and the other eight rabbits were injected with a 2 per cent. alcoholic pancreatin salt solution. I injected intravenously 5 c.c. or less of 1 per cent. native pancreatin to 1 kg. of body weight of each rabbit, because any amount over 5 c.c. seemed to be lethal when given intravenously; however, rabbits could resist a 2 per cent. alcoholic pancreatin, about twice the dose of native pancreatin. The injected rabbits were killed at intervals for histologic examination; that is, 4 rabbits were killed at thirty minutes after the injection of the native pancreatin, 3 rabbits at one hour, 4 at one and one-half hours, 3 at two hours, 1 each at two and one-half, six, twelve, and twenty-four hours, 2 at thirty-eight hours, 3 at forty-eight hours, 2 at fifty-two hours, and 1 at each sixty and seventy-two hours; and also 1 each at thirty minutes, one hour, one and one-half hours, three hours, twenty-four hours, and forty-eight hours after the injection of the alcoholic pancreatin.

Procedure for making the pancreatic ferments solutions:

1. *Unmodified pancreatic ferments solutions.*—Commercial pancreatin (P. D. & Co), trypsin (Central Scientific Supply Company) and amylopsin (Digestive Ferments Company) powders were added to physiologic sodium chlorid solution in the amount of 1 per cent. by weight. After repeated shaking the solutions were filtered through hard-pressed filters and finally through Berkefeld candles. The resulting filtrate was clear and sterile.

2. *Alcohol modified pancreatic ferment solutions.*—Ten per cent. solutions of the ferments mentioned were made in physiologic sodium chlorid solution, and after thorough shaking were filtered through hard-pressed paper. To the resulting filtrate were added 20 volumes of absolute alcohol and the mixture allowed to stand thirty minutes, with the formation of a white precipitate resulting. The mixture was then centrifugalized and the sediment rapidly resuspended in an amount of salt solution making the concentration 2 per cent. relative to the amount of pancreatic ferments originally employed.

All of the rabbits experimented on showed such physical symptoms as trembling, uneasiness, difficulty in walking, dyspnea and strong palpitation of the heart, and sometimes shock a short time after the injection; however, in the case of the alcohol modified pancreatin the degree of these symptoms was much less than in the animals given native pancreatin, corresponding to Lombroso's observation on pancreatic juice.

B. PATHOLOGIC CHANGES

1. *The Production of Hyperemia, Hemorrhage and Thrombosis.*—Thirty-three rabbits were employed, twenty-seven of which were intravenously injected once with native pancreatin. The other six rabbits were injected with an alcoholic solution of pancreatin. These rabbits were killed for anatomic observation.

8. Jobling, Petersen and Eggstein: J. Exper. M. 22: 1915, No. 2.

The rabbits developed more or less hyperemia, hemorrhage and thrombosis throughout the body in almost all instances, but the production of thrombosis was mainly found in liver and lung, although kidney and bone marrow showed it in a few cases. Hemorrhagic inflammation seemed to be markedly produced after one hour following the injection of antigen. The hemorrhagic foci showed a condition of absorption at thirty-eight hours after the injection. This hemorrhagic phenomenon was produced not only in liver, spleen, lung, kidney, bone marrow, heart muscle, pancreas and suprarenal capsule, but also in the abdominal cavity in four cases, in the omentum in five cases, in the urine in one case, in the abdominal muscles in three cases, and in the superficial muscles of the thigh in two cases.

In the alcoholic pancreatin cases the anatomic changes were almost the same as in the cases of native pancreatin injection, even though the physical symptoms, compared with the former, indicated less toxicity.

Of these inflammations, there were found in many cases an infiltration of small round cells in Glisson's capsule and atrophy of the liver cells, which latter was due, no doubt, to the pressure of the hemorrhage. This was noticeable in one case in particular in which the animal was killed fifty-four hours after the injection. In the kidneys the hemorrhagic lesions were found chiefly in the glomeruli and in Henle's loop. Hyaline casts were also found in many cases. The kidneys presented an acute hemorrhagic nephritis, so that the urines indicated a markedly positive protein reaction of the rabbits which were killed before forty-eight hours after the injection. The protein reaction, however, was not found in the rabbits killed after fifty-four hours following the injection. In the pancreas the hemorrhagic lesions were marked in the islands of Langerhans, although they were found in other parts.

On the coagulation time of the blood after the injection of enzymes, as in Hildebrandt's and Piquet's observations on various enzymes, I also found delay in two cases of twenty-seven injected intravenously with native pancreatin. In animals killed at two and forty-eight hours after the injection coagulation of the blood was very slow.

C. PATHOLOGIC CHANGES IN RABBITS IMMUNIZED WITH PANCREATIN

In 1899, Schepilewsky⁹ produced extensive subcutaneous necrosis and suppuration by the injection of various kinds of ferments, such as lab ferment, pancreatin, papayotin, etc., and succeeded in causing an amyloid degeneration in rabbits; that is, two (in spleen, intestine

9. Schepilewsky: *Centralbl. f. Bakteriol.* 25: 1899.

and liver) of seven cases with lab ferment, one (in spleen) of six cases with pancreatin, and one (in spleen) of two cases with papayotin; he concluded that the injection of these enzymes caused hyaline degeneration more frequently than amyloid degeneration. In 1903, Wells¹⁰ observed fat necrosis in the omentum and mesentery of dogs and cats after the intraperitoneal injection of pancreatin. He concluded that the lipase in pancreatin may be the agent causing the fat necrosis. This phenomenon can be produced with constancy in dogs and cats, but less successfully in rabbits.

I also observed various pathologic changes in experimental rabbits immunized with pancreatin.

For this experiment I employed twelve rabbits immunized with native or an alcoholic pancreatin.

As already shown in the foregoing experiments toxicity was produced in the rabbits by the injection of the antigen up to five or six injections; however, the toxicity decreased after the promoting of the immune process in the rabbits. This phenomenon was found more marked after intravenous than after subcutaneous or intraperitoneal injections. By subcutaneous injection there was produced an abscess at the site of the injection, but no fat necrosis intraperitoneally. In intravenous injections, if a small amount of the antigen reaches the extravascular tissue it produces locally an acute inflammation followed by gangrene. In addition, some of these rabbits developed during the immunization a crippled condition in the fore legs or hind legs, especially in the hind legs, together with a loss of body weight.

In the histologic examination I found many pathologic changes in the organs, as shown in the following protocol.

PROTOCOL

EXPERIMENT 2.—*Macroscopic anatomic changes in rabbits immunized with native pancreatin.*—In this experiment three rabbits were employed.

Rabbit 11 (Male).—Total amount of antigen injected, 100 c.c. of 1 per cent. pancreatin (injected seven times intravenously and three times peritoneally)—1 gm.; animal killed on the sixty-first day after the first injection (eighth day after the last injection); there was found no loss of body weight.

Necropsy.—All organs seemed in normal condition.

Rabbit 24 (Female).—Total amount of antigen injected, 72 c.c. of 1 per cent. pancreatin (injected nine times into the ear vein)—0.72 gm.; killed on the fifty-first day after the first injection (tenth day after the last injection); there was sometimes produced an acute inflammation followed by necrosis, which was due to the small amount of antigen that went into the extravascular tissues of the external part of the ear during the immunization; a crippled condition was found in the left fore leg on the fifty-first day and in the hind legs on the fifty-fourth day after the first injection; body weight was markedly decreased.

Necropsy.—An enlargement of the spleen was found; the bone marrow of the legs showed a yellow, grayish-white color, and a moderate hardening, especially of the hind legs.

10. Wells: J. M. Res. 9: 1903.

Rabbit 25 (Female).—Total amount of antigen injected, 80 c.c. of 1 per cent. pancreatin (injected ten times into the ear vein)—0.8 gm.; killed on the fifty-sixth day after the first injection (tenth day after the last injection); a crippled condition in the hind legs was found on the forty-eighth day after the first injection; in this case also an acute inflammation followed by gangrene was sometimes produced in the extravascular tissue of the external part of the ear where the antigen was injected intravenously; body weight was markedly decreased.

Necropsy.—An enlargement of the spleen and both suprarenal glands was found; also hardness of the bone marrow of both hind legs, which was brownish white in color; there was no change in the bone marrow of the fore legs. Large abscesses were found in the subcutaneous tissue surrounding both hip joints; the lesions were old, showing softness in consistence and a milky white color.

EXPERIMENT 3.—*Macroscopic anatomic changes in rabbits immunized with an alcoholic pancreatin solution.*—Six rabbits were employed in this experiment.

Rabbit 1 (Male).—Total amount of the antigen injected, 95 c.c. of a 2 per cent. alcoholic pancreatin (injected ten times intravenously and once peritoneally)—1.9 gm.; died on the fifty-fourth day after the first injection (eighth day after the last injection); a crippled condition was found in both hind legs on the thirty-sixth day after the first injection; body weight was markedly decreased.

Necropsy.—A slight enlargement of the spleen was found; hardness of the bone marrow of both hind legs, and a yellowish-gray color and also a slight hardness and a brownish gray in color of that of the both fore legs.

Rabbit 2 (Female).—Total amount of the antigen injected, 110 c.c. of a 2 per cent. alcoholic pancreatin (injected ten times into the ear vein and twice peritoneally)—2.2 gm.; killed on the sixty-third day after the first injection (eighth day after the last injection); there was produced an acute inflammation followed by necrosis on the external part of the ear where some of the antigen injected intravenously entered the extravascular tissue; body weight was slightly decreased.

Necropsy.—A slight enlargement of the spleen and both suprarenal glands; hardness and a grayish-white color of the bone marrow of the legs.

Rabbit 4 (Male).—Total amount of the antigen injected, 108 c.c. of a 2 per cent. alcoholic pancreatin (injected eleven times intravenously and once peritoneally)—2.16 gm.; killed on the sixty-first day after the first injection (eighth day after the last injection); body weight slightly decreased.

Necropsy.—An enlargement of the spleen; hardness and a grayish-white color of the bone marrow of both hind legs but no change of that of the fore legs.

Rabbit 5 (Male).—Total amount of the antigen injected, 77 c.c. (injected ten times intravenously and twice peritoneally)—1.54 gm.; killed on the sixty-first day after the first injection (eighth day after the last injection); a crippled condition was found in the left hind leg on the forty-ninth day after the first injection; body weight was markedly decreased.

Necropsy.—Body markedly emaciated; a hemorrhagic infarct of the lower lobe of the left lung, and a hemorrhage of the lower lobe of the right lung; jaundice; that is, liver, fat tissue of the mesentery, conjunctivae and urine were yellow in color; hardness and a yellow-grayish white color of the bone marrow of the left hind leg; the urine showed positive for bile pigment by Gmelin's method.

Rabbit 6 (Female).—Total amount of antigen injected, 104 c.c. of a 2 per cent. alcoholic pancreatin (injected three times intravenously, three times subcutaneously and five times peritoneally)—2.08 gm.; killed on the sixty-fifth day after the first injection (tenth day after the last injection); a tumor was found on the sixteenth day after the injection, in the subcutaneous tissue of

the abdominal wall where the antigen was injected subcutaneously; this tumor was the size of a nut and of a moderate hardness; body weight was not changed.

Necropsy.—Enlargement of the spleen and both suprarenals; hardness of the bone marrow of the thighs of both hind legs, but no change of that of the lower legs. The tumor in the abdominal wall was of a yellowish, milky-white color and sticky, but had no odor.

Rabbit 8 (Male).—Total amount of antigen injected, 64 c.c. of a 2 per cent. alcoholic pancreatin (injected seven times intravenously and twice peritoneally)—1.28 gm.; killed on the fifty-sixth day after the first injection (ninth day after the last injection); body weight slightly decreased.

Necropsy.—An enlargement of the spleen; no change of the bone marrow.

EXPERIMENT 4.—*Macroscopic anatomic changes in rabbits immunized with a native and an alcoholic pancreatin.*—In this experiment three rabbits were employed.

Rabbit 3 (Female).—Total amount of antigen injected, 15 c.c. of a 1 per cent. native pancreatin (three times intravenously), and 42 c.c. of a 2 per cent. alcoholic pancreatin (eight times intravenously)—0.99 gm. altogether; killed on the sixty-third day after the first injection (eighth day after the last injection); body weight was slightly decreased.

Necropsy.—Body was emaciated; enlargement of the spleen and both suprarenals; liver cirrhosis; no change in the bone marrow.

Rabbit 9 (Female).—Total amount of antigen injected, 27 c.c. of 1 per cent. native pancreatin (three times intravenously) and forty-one c.c. of 2 per cent. alcoholic pancreatin (twice intravenously and three times peritoneally)—1.09 gm.; killed on the sixty-first day after the first injection (eighth day after the last injection); a crippled condition was found in the left hind leg on the twenty-first day after the first injection; body weight was not changed.

Necropsy.—All organs seemed in normal condition.

Rabbit 10 (Female).—Total amount of the antigen injected, 24 c.c. of a 1 per cent. native pancreatin (three times intravenously) and 36 c.c. of a 2 per cent. alcoholic pancreatin (twice intravenously and three times peritoneally)—0.96 gm.; killed on the sixty-first day after the first injection (eighth day after the last injection); body weight was moderately increased.

Necropsy.—An enlargement of the spleen; the other organs seemed in normal condition.

Histologic Examination.—Materials obtained from the necropsies were fixed in Zenker's fluid and formaldehyd solution, and sections were prepared by the paraffin and frozen section methods. These sections were treated with the following staining solutions:

1. Hematoxylin-eosin.
2. Van Gieson's picro-fuchsin and iron-hematoxylin.
3. Gentian-violet.
4. Malachite-green, acid fuchsin, and martius yellow (Pianese's¹¹ staining solution for the differentiation of hyalin, colloid, mucin and a substance resembling amyloid).
5. Sudan III-hematoxylin (employed for the liver, kidneys, spleen myocardium and lungs).

The following results were obtained microscopically:

Liver: All the livers of twelve rabbits showed a greater or less increase in Periportal and Glisson's capsule connective tissue with an infiltration of small round cells in those areas; in addition, Rabbit 1 showed many hemorrhagic lesions; Rabbits 3 and 5 showed many thrombi in the smaller portal veins and hyaline degeneration of some of these thrombi; Rabbit 8 showed a typical liver cirrhosis.

11. Pianese: Mallory and Wrights Pathological Technique, Ed. 6, 1915, p. 306.

The media of median portal veins of the liver stained a deep blue with hematoxylin-eosin in Rabbit 25.

Tawara,¹² in 1913, also found such a substance stained a deep blue with hematoxylin-sudan in the intima of some arteriosclerotic vessels, and he decided that the substance was hyalin. The substance found in the media of the portal veins in my experiment, therefore, corresponds to his substance found in the intima by staining; also the substance in my experiment stained a brick-red color with Pianese's solution, so that this change of the media of the portal veins probably is a hyaline degeneration.

Liver cells surrounding the acini in most cases, and also those surrounding the portal veins in some other cases, presented, in general, a slight swelling; however, the cells of one case (Case 24) were vacuolated and in a degenerated condition; that is, the cells stained an intense red with eosin, but in opacity resembled hyaline degeneration; they also stained a yellowish brown with Van Gieson's picro-fuchsin. The liver cells of five rabbits (3, 4, 8, 24 and 25) were stained a dark reddish violet with gentian-violet. Those of other rabbits (5, 9 and 10) were stained a brick-red in some cells and (slightly) a dark reddish violet in others, but a dark green with gentian-violet. Those of three other rabbits (1, 2 and 6) stained a brick red with Pianese's staining solution, and a dark green with gentian-violet, while the liver cells of Rabbit 11 seemed in a normal condition.

Considering the degeneration of liver cells from the results of staining, the cells of five rabbits (3, 4, 8, 24 and 25) the condition seemed to be neither a hyaline, colloid nor a typical amyloid degeneration, but seemed to be an "amyloid-like" degeneration, while the liver cells of three other rabbits (5, 9 and 10) were certainly in an intermediary condition between hyaline and amyloid degeneration; and also those of three other rabbits (1, 2 and 6) were in a state of hyaline degeneration. The degeneration of these liver cells was most marked in two rabbits (24 and 25), moderate in six rabbits (3, 4, 5, 6, 8, 9 and 10), and slight in three rabbits (1, 2, and 6); especially the liver cells of the Rabbits 24 and 25 were markedly swollen and some nuclei were displaced or had disappeared. Frozen sections of these liver tissues were also stained with sudan III and in all cases showed a positive reaction. The positive reaction of sudan III for fatty degeneration was shown in the instance of a slight degeneration in the liver cells surrounding the acini and in the Kupffer cells; however, it was best exhibited in marked degeneration in areas of acini and in Glisson's capsule. The degree of fatty degeneration was moderate in nine rabbits (1, 2, 3, 4, 5, 9, 11, 24 and 25) and marked in three rabbits (6, 8 and 10).

Kidneys: The kidneys also showed greater or less degenerative changes in the tubular epithelium in all cases, suggesting a granular degeneration, but most marked in the convoluted tubules; some desquamation of tubular and glomerular epithelium; formation of casts; a slight hyperemia; some interstitial infiltration with small round cells; a slight cellular proliferation of connective tissue, and also hemorrhagic lesions, in some cases showing an acute or subacute parenchymatous degeneration and glomerulitis.

Some of the epithelial cells of the convoluted tubules and glomeruli were stained an intense red color with eosin, resembling hyaline degeneration; in some cases they were stained a dark red with Pianese's staining solution, a slight reddish violet with gentian-violet and a yellowish brown with Van Gieson's picro-fuchsin. The cells of six (1, 3, 5, 6, 11 and 25) of twelve rabbits, were most marked in the convoluted tubules, being stained a dark red with Pianese's solution and a slight reddish violet with gentian-violet. In one case (6) of these six rabbits hyalin-like substance was found as large masses in the glomeruli; in two other cases (2 and 4) of twelve rabbits two kinds of degeneration were shown in the epithelial cells of the convoluted tubules and glomeruli. Some epithelial cells were stained a brick-red color with

12. Tawara: *Verhandl. d. Jap. path. Gesellsch.* 3: 1913.

Pianese's solution but a dark green with gentian-violet, and some were of a dark-red color with Pianese's solution and a slight reddish violet with gentian-violet; in three other cases (8, 9 and 10) they were stained a brick red with Pianese's solution and a dark green with gentian-violet, while in one case (24) there was not found any special staining reaction with Pianese's solution and gentian-violet.

In summary, the degenerated epithelial cells, therefore, showed an amyloid-like degeneration in six rabbits (1, 3, 5, 6, 11 and 25), a hyaline and an amyloid-like degeneration in two rabbits (2 and 4), and a hyaline degeneration in three other rabbits (8, 9 and 10).

Frozen sections stained with sudan III showed, in general, a fatty degeneration in all the cases, affecting principally the convoluted tubules, although the glomeruli were slightly affected. The degree of this degeneration was slight in two cases (3 and 9), moderate in six other cases (1, 2, 4, 5, 11 and 25) and strong in four more cases (6, 8, 10 and 24).

Spleen: The spleens showed, in general, a moderate increase of phagocyte and giant cells in the pulp, and also an increase of lymphoid tissue and the connective tissue framework; hyperemia in all cases, and some hemorrhagic lesions in other cases.

Some special pathologic changes presented a hyalin-like substance in the pulp or malpighian bodies, which stained a dark-red color with Pianese's solution, and a dark green with gentian-violet. The deposit of this substance was recognized in ten cases (1, 2, 3, 4, 5, 6, 9, 10, 24 and 25) out of twelve rabbits; however, it was most remarkable in three (3, 4 and 5) of these cases, especially in Rabbit 3, in which the hyalin-like substance was deposited in the endothelial cells of a capillary in a malpighian body, but was not found in the other cases.

The hyalin-like or amyloid-like degeneration of the cells of the spleen was principally recognized in macrophages and giant cells, and also slightly in endothelial cells of the reticular tissue, while in two cases of Rabbits 8 and 10 no such change was recognized. The frozen sections, stained with sudan III, showed a positive result in all the cases; that is, very slight in one case (25), slight in eight other cases (1, 2, 3, 8, 9, 10, 11 and 24), moderate in two cases (4 and 5) and strong in one case (6).

Heart Muscle: The heart muscle of six rabbits (2, 3, 9, 10, 11 and 24) showed hemorrhagic lesions; some increase of interstitial connective tissue in two rabbits (2 and 8), and some atrophy in five rabbits (2, 8, 9, 10 and 11). Some pathologic changes took an intensely red color with cosin, and a slightly reddish violet with Pianese's solution, but a dark green with gentian-violet, showing moderately an amyloid-like degeneration in five rabbits (3, 4, 8, 9 and 10). There were a hyalin-like degeneration in five other rabbits (2, 5, 6, 11 and 25), while there was no such change in two cases (1 and 24).

Frozen sections stained with sudan III showed a fatty degeneration in all the cases; very slight in eight rabbits (1, 2, 3, 8, 9, 11, 24 and 25), moderate in three rabbits (4, 5 and 10) and strong in one rabbit (6).

Lungs: The lungs showed some increase of interstitial connective tissue accompanied by infiltration of small round cells in ten cases (1, 2, 3, 4, 8, 9, 10, 11, 24 and 25); in twelve rabbits a moderate hyperemia in five cases (1, 2, 6, 9 and 11), and some hemorrhagic lesions in two cases (5 and 24). Rabbit 5 showed a marked hemorrhagic infarct, a thickening of the intima and some increase of the media of some of the smaller or medium sized pulmonary arteries in four cases (5, 11, 24 and 25), and some thrombi in the capillaries in three cases (3, 24 and 25). A hyalin-like or an amyloid-like degeneration, as found in other organs, was not at all present with special stains. Frozen sections stained with sudan III showed no fatty degeneration.

Bone Marrow: The necropsies on seven rabbits (1, 2, 4, 5, 6, 24 and 25) showed amyloid degeneration, and five other rabbits (3, 8, 9, 10 and 11) showed a normal condition. Twelve rabbits showed histologically a pathologic con-

dition. Seven rabbits (1, 2, 4, 5, 6, 24 and 25) showed a necrotic condition of marrow cells and also five more rabbits (3, 8, 9, 10 and 11) showed, in general, a degenerative condition of marrow cells but an entirely necrotic condition showing karyolysis and karyorhexis at some parts. Fibrous and reticular tissue was fairly proliferated, especially in three rabbits (1, 5 and 25), together with cicatricial tissue. These marrow cells generally stained an intensely red color with eosin, a reddish violet with a gentian-violet and a slight reddish-violet color with Papanicolaou's solution, especially the giant cells and large marrow cells, and also a yellowish brown with Van Gieson's picro-fuchsin.

Pancreas: The pancreas in all the cases were in almost a normal condition; however, a slight hyperemia was found in three cases (1, 6 and 11), and also a slight increase of the interstitial connective tissue in four cases (3, 8, 9 and 11).

Suprarenal Glands: The adrenals of all the animals were in normal condition.

D. COMPARATIVE STUDIES ON THE PATHOLOGY OF PANCREATIN, TRYPSIN AND AMYLOPSIN

For this experiment I employed seven rabbits immunized with a native or an alcoholic trypsin and amylopsin. The clinical symptoms produced in rabbits were just the same as in the instance of the pancreatin. It is not necessary to go into detail in regard to the toxicity of the trypsin and amylopsin.

PROTOCOLS OF EXPERIMENTS

EXPERIMENT 5.—*Macroscopic anatomic changes of rabbits immunized with a native trypsin.*—In this experiment two rabbits were employed.

Rabbit 20 (Male).—Total amount of antigen injected, 75 c.c. of a 1 per cent. trypsin (injected eight times intravenously and once peritoneally)—0.75 gm.; killed on the forty-second day after the first injection (eighth day after the last injection); body weight was slightly decreased.

Necropsy.—A slight jaundice (a slight yellow color of liver, intestine and urine). The urine was positive for bile pigment by Gmelin's test.

Rabbit 21 (Female).—Total amount of antigen injected, 85 c.c. of a 1 per cent. trypsin (injected eight times intravenously and once peritoneally)—0.85 gm.; killed on the one hundred and nineteenth day after the first injection (eighty-sixth day after the last injection); body weight was slightly decreased up to the last injection; however, afterward it gradually increased.

Necropsy.—An enlargement of the spleen and both kidneys; congestion of the kidneys and bone marrow; a remarkable yellow color of the liver.

EXPERIMENT 6.—*Macroscopic anatomic changes in rabbits immunized with alcoholic trypsin.*—In this experiment one rabbit was used.

Rabbit 22 (Female).—Total amount of the antigen injected, 51 c.c. of a 2 per cent. alcoholic trypsin (injected eight times intravenously and once peritoneally)—1.02 gm.; killed on the one hundred and nineteenth day after the first injection (eighty-sixth day after the last injection); body weight slightly decreased up to the last injection, but later gradually increased.

Necropsy.—A remarkable yellow color of the liver; congestion of the bone marrow.

EXPERIMENT 5.—*Macroscopic anatomic changes in rabbits immunized with native amylopsin.*—In this experiment two rabbits were employed.

Rabbit 16 (Male).—Total amount of antigen injected, 87 c.c. of 1 per cent. amylopsin (injected eight times intravenously and once peritoneally)—0.87 gm.; killed on the one hundred and twenty-first day after the first injection (eighty-

sixth day after the last injection); there was almost no change in the body weight.

Necropsy.—An enlargement of the suprarenal glands; a yellow color of the liver and myocardium; hardness of the bone marrow of both thighs and showing a yellow-gray color.

Rabbit 17 (Female).—Total amount of the antigen injected, 82.5 c.c. of 1 per cent. amylopsin (injected eight times intravenously and once peritoneally); killed on the forty-fourth day after the first injection (ninth day after the last injection); body weight was gradually decreased.

Necropsy.—Congestion of the lower lobes of both lungs, kidneys and spleen; hardness of bone marrow of both thighs, showing a grayish-white color.

EXPERIMENT 8.—*Macroscopic anatomic changes in rabbits immunized with alcoholic amylopsin.*—In this experiment two rabbits were employed.

Rabbit 18 (Male).—Total amount of antigen injected, 67.5 c.c. of 2 per cent. alcoholic amylopsin (injected eight times intravenously and once peritoneally)—1.35 gm.; killed on the forty-fourth day after the first injection (ninth day after the last injection); body weight was slightly increased.

Necropsy.—Congestion of the lower lobes of both lungs; hemorrhagic infarct of the spleen; no change in the bone marrow.

Rabbit 19 (Female).—Total amount of antigen injected, 71.5 c.c. of 2 per cent. alcoholic amylopsin (injected eight times intravenously and once peritoneally)—1.43 gm.; killed on the one hundred and twenty-first day after the first injection (eighty-sixth day after the last injection); body weight was slightly decreased up to the last injection; however, it afterward gradually increased.

Necropsy.—All organs seemed in normal condition.

Histological Examination.—Materials obtained at necropsy from all the animals were treated the same as in the instance of the pancreatin.

A. The findings in the case of the rabbits immunized with trypsin were as follows:

Liver: The livers of three rabbits showed a greater or less increase in periportal and Glisson's capsule connective tissue, with an infiltration of small round cells in those areas, Rabbit 21 especially showing a typical liver cirrhosis, and also Rabbit 20 showing a slight congestion. Liver cells surrounding the acini in all cases showed some degenerative condition in the cases of Rabbits 21 and 22 especially, staining an intensely red color with eosin, a dark reddish violet with Pianese's solution, and a yellowish brown with Van Gieson's picro-fuchsin, while a dark green was produced with gentian-violet, thus showing an amyloid-like degeneration. Frozen sections stained with sudan III showed a fatty degeneration, moderate in two cases (20 and 21) and strong in one case (22).

Kidneys: The kidneys presented a greater or less degenerative change in the tubular epithelium in all cases, showing granular degeneration especially marked in the convoluted tubules; and also some desquamation of tubular and glomerular epithelium, formation of casts, a slight hyperemia and some increase of the interstitial connective tissue, with an infiltration of small round cells.

Some epithelial cells of the convoluted tubules and glomeruli were stained an intensely red color with eosin, a dark-red color with Pianese's solution, and a yellowish brown with Van Gieson's picro-fuchsin, but a dark green with gentian-violet, indicating an amyloid-like degeneration of these cells. This change was markedly present in two cases, Rabbits 21 and 22, while in one case, Rabbit 20, it looked similar to hyaline degeneration.

Frozen sections stained with sudan III showed fatty degeneration, very slight in Rabbit 20, moderate in Rabbit 21, and strong in Rabbit 22.

Spleen: The spleens showed a moderate increase of phagocytes and giant cells in the pulp, the lymphoid tissue and the connective tissue framework, with hyperemia in all cases.

In the special pathologic changes there was presented a hyalin-like or an amyloid-like substance in the pulp or malpighian bodies, which stained an intensely red color with eosin in all cases, a dark-red color or a slight reddish violet with Pianese's solution in two cases (Rabbits 21 and 22), but a brick color in one case (Rabbit 20), a yellowish brown with Van Gieson's picro-fuchsin and a dark green with gentian-violet, thus showing an amyloid-like degeneration in two cases (21 and 22) and a hyalin-like degeneration in one case (20).

Such a change was chiefly recognized in phagocytic and giant cells and also slightly in endothelial cells of reticular tissue.

Frozen sections stained with sudan III showed a slight fatty degeneration in two cases (20 and 21), and moderate in one case (22).

Myocardium: The myocardium in all cases showed some hemorrhagic lesions, some increase of the interstitial connective tissue, some atrophy in one case (22), and some hyalin-like degeneration which stained an intensely red color with eosin, a brick color with Pianese's solution and a dark green with gentian-violet.

Frozen sections stained with sudan III showed fatty degeneration in all cases.

Lungs: The lungs showed some increase of interstitial connective tissue and an infiltration of small round cells, some hyperemia, and thrombosis of the smaller pulmonary veins in all cases, and a marked thickening of the intima and some increase of the media of smaller or medium sized pulmonary arteries in two cases (20 and 21), with no pathologic changes in the cells.

Frozen sections stained with sudan III showed no fatty degeneration.

Bone Marrow: The bone marrow showed a slight hyperemia in all the cases; in two cases (20 and 21) there was, in general, a normal condition of marrow cells, although there was present a slight hyalin-like degeneration of a few large marrow cells and giant cells. In one case (22) there were observed necrotic areas and some granulation tissue in such areas. There were also present many large marrow and giant cells in an amyloid-like degeneration, staining an intensely red color with eosin, a slight reddish violet with Pianese's solution and gentian-violet, and also a yellowish brown with Van Gieson's picro-fuchsin.

Pancreas: The pancreas in all the cases were in almost normal condition although a slight hyperemia was found.

Suprarenal Glands: All adrenals were in a normal condition.

B. The findings in rabbits immunized with the amylopsin were as follows:

Liver: The livers of four rabbits showed a greater or less increase of periportal and Glisson's capsule connective tissue, with an infiltration of small round cells and a slight hyperemia. Rabbit 16, showed some thickening of the intima, together with an increase of the media of the smaller hepatic arteries. Rabbits 17 and 18 showed an increase of bile ducts. The liver cells surrounding the acini in all the cases showed some degeneration, especially remarkable in the cases of Rabbits 16 and 19; staining an intensely red color with eosin, a dark reddish violet with Pianese's solution, a yellowish brown with Van Gieson's picro-fuchsin, and a dark green with gentian-violet, just suggesting an amyloid-like degeneration.

Frozen section stained with sudan III showed considerable fatty degeneration in all the cases.

Kidneys: The kidneys showed a greater or less degenerative change in the tubular epithelium in all the cases, a granular degeneration, especially remarkable in the convoluted tubules, some desquamation of tubular and glomerular epithelium, formation of casts, a slight hyperemia and some increase in the interstitial connective tissue, with an infiltration of small round cells. Rabbit 17 showed some thickening of the intima, together with an increase of the media of the smaller renal arteries.

Some epithelial cells of the convoluted tubules and glomeruli, especially the convoluted tubules of three rabbits (16, 17 and 19) were stained an intensely

red color with eosin, a dark reddish violet with Pianese's solution, a yellowish brown with Van Gieson's picro-fuchsin, and a dark green with gentian-violet, indicating an amyloid-like degeneration of the epithelial cells. Rabbit 18 showed no such change.

Frozen sections stained with sudan III showed a marked fatty degeneration in all the cases.

Spleen: The spleens showed an increase of phagocyte and giant cells in the pulp, the lymphoid tissue and connective tissue framework, and some hyperemia in all the cases. Rabbit 16 showed some thickening of the intima of the smaller splenic arteries. No other special change was present in all the cases. Frozen sections stained with sudan III showed a marked fatty degeneration in one case (16) and slight in three cases (17, 18 and 19).

Myocardium: The heart muscle in all the cases showed some hemorrhagic lesions, and some thrombosis in one case (16); and a hyaline degeneration of the myocardium in one case (17), which stained an intensely red color with eosin and a brick-red color with Pianese's solution. In three other rabbits no such change was present.

Frozen sections stained with sudan III showed much fatty degeneration in all the cases.

Lungs: The lungs showed some increase of the interstitial connective tissue, with an infiltration of small round cells and some hyperemia in all the cases. Marked thickening of the intima and some increase of the media of the smaller or the medium sized pulmonary arteries were found in three cases (16, 17, and 18), and also an amyloid-like degeneration of the media of the medium pulmonary arteries in one case (19), which showed a characteristic staining reaction with eosin and Pianese's solution, as in the other instances.

Frozen sections stained with sudan III showed no fatty degeneration.

Bone Marrow: The bone marrow of two cases (16 and 17) showed some necrosis. The large marrow cells and giant cells of all the cases showed generally an amyloid-like degeneration, especially remarkable in two cases (16 and 17), and a characteristic staining reaction with eosin and Pianese's solution and gentian-violet, as in the other instances.

Pancreas: The pancreas of Rabbit 16 showed a hyalin-like degeneration of the epithelial cells of the islands of Langerhans, and also a slight hyperemia in two cases (16 and 17), while the other two cases (18 and 19) were in a normal condition.

Suprarenal Glands: All adrenals were in a normal condition.

E. ON THE PRODUCTION OF THE HYALINE AND "AMYLOID-LIKE" DEGENERATION IN RABBITS BY THE INJECTION OF PANCREATIN, TRYPSIN AND AMYLOPSIN

Since Frisch,¹³ in 1877, announced the experimental production of an amyloid-like substance in the cornea of rabbits injected in the cornea with fresh blood from a case of anthrax, we have a majority of investigations on the production of experimental amyloidosis with such materials as turpentine (Czerny,¹⁴ Lubarsch,¹⁵ Nowak¹⁶),

13. Frisch: Sitzungsber. d. k. Akad. d. Wissensch. Math. Naturw. Cl., Abt. 3, 76: 1877.

14. Czerny: Arch. f. exper. Path. u. Pharmacol. 31: 1893.

15. Lubarsch: Virchows Arch. f. path. Anat. 150: 1897.

16. Nowak: Virchows Arch. f. path. Anat. 153: 1898.

B. pyocyaneus (Bouchard-Charrian,¹⁷ Krakow¹⁸), *B. tuberculosis* (Bouchard-Charrian¹⁷), *Staphylococcus aureus* (Krakow,¹⁸ Davidsohn,¹⁹ Maximow,²⁰ Dantschakow,²¹ gonococcus (Davidsohn¹⁹), fresh and sterile pus (Nowak¹⁶), *B. pestis* (Schoukewitsch²²), *B. coli* (Bailey²³), diphtheria toxin (Zenoni²⁴), Pease-Pearce,²⁵ Lewis,²⁶ typhoid toxin (Lewis²⁶), tuberculin (Nowak¹⁶), and lab ferment, papayotin and pancreatin (Schepilewsky⁹).

I could not find any report on the production of amyloidosis by pancreatin except Schepilewsky's experiment. He succeeded in producing an amyloidosis in the spleen in one experiment in six rabbits injected with pancreatin. He concluded that a hyaline degeneration caused more than an amyloid degeneration. I also produced a hyaline and an amyloid-like degeneration in rabbits injected with pancreatin, trypsin, and amylopsin as shown in the foregoing statement. An amyloid-like degeneration was produced in the livers of five rabbits (3, 4, 8, 24 and 25), in the kidneys of six rabbits (1, 3, 5, 6, 11 and 25), in the myocardium of five cases (3, 4, 8, 9, 10), and in the bone marrow in all the cases, especially marked in seven cases (1, 2, 4, 5, 6, 24 and 25), which stained a dark reddish-violet color with Pianese's solution, a slight reddish violet with gentian-violet, an intense red with eosin and a yellowish brown with Van Gieson's picro-fuchsin. Both the hyalin-like and amyloid-like degeneration in the livers of three rabbits (5, 9 and 10), and in the kidneys of two cases (2 and 4) stained a brick red and a slight dark reddish violet, or a dark red, with Pianese's solution, a dark green with gentian-violet and almost the same with eosin and van Gieson's picro-fuchsin as in the amyloid-like degeneration. A hyalin-like degeneration in the livers of three cases (1, 2 and 6), in the kidneys of three cases (8, 9 and 10), and in the myocardium of five cases (2, 5, 6, 11 and 25) stained a brick-red color with Pianese's solution, but a dark green with gentian-violet and almost the same with eosin and Van Gieson's picro-fuchsin as in the amyloid-like degeneration. An intermediary condition between the hyalin-like and amyloid-like degeneration in the spleen of ten cases (1, 2, 3, 4, 5, 6, 9, 10, 24 and 25) stained a dark red with Pianese's

17. Bouchard-Charrian: Compt. rend. Soc. de biol. **5**: 1888.

18. Krakow: Centralbl. f. allg. Path. u. path. Anat. **6**: 1895; Arch. de méd. exper. **8**: 1896; Arch. f. exper. Path. u. Pharmacol. **40**: 1898.

19. Davidsohn: Virchows Arch. f. path. Anat. **150**: 1897; Verhandl. d. Deutsch. path. Gesellsch. **7**: 1904; Ergebn. d. allg. Path. u. path. Anat. **12**: 1908; Virchows Arch. f. path. Anat. **192**: 1908.

20. Maximow: Virchows Arch. f. path. Anat. **153**: 1898.

21. Dantschakow: Virchows Arch. f. path. Anat. **187**: 1906.

22. Schoukewitsch: Arch. d. sc. biol. **12**: 1907.

23. Bailey: J. Exper. M. **23**: 1916, No. 6.

24. Zenoni: Centralbl. f. allg. Path. u. path. Anat. **13**: 1902.

25. Pease-Pearce: J. Infect. Dis. **3**: 1906.

26. Lewis: J. M. Res. **15**: 1906.

solution, a dark green with gentian-violet. Eosin and Van Gieson's picro-fuchsin stained them as in the other degenerative cases, as also a hyaline degeneration of the media of the medium-sized portal veins of the liver in one case (25), and also a larger hyaline mass in the glomeruli of the kidney of one case (6) of twelve rabbits injected with pancreatin intravenously. There was no such change present in the liver in one case (11), in the kidneys of one case (24), in the spleen of two cases (8 and 11) and in the myocardium of two cases (1 and 24), or in the lungs, adrenals, and pancreas of all the cases.

By the injection of trypsin there was also produced an amyloid-like degeneration of the liver and bone marrow of all the cases, an intermediary degeneration between the hyalin-like and amyloid-like degeneration in the spleen of two cases (21 and 22), and a hyalin-like degeneration in the spleen of one case (20), and in the myocardium of all the cases (three rabbits), while no such degeneration was found in the lungs, adrenals or the pancreas of all the cases; by the injection of amylopsin, amyloid-like degeneration was produced in the kidneys of three rabbits (16, 17 and 19), in the bone marrow of all the cases and in the media of the medium pulmonary arteries in one case (19). A degeneration intermediary between the hyalin-like and amyloid-like degeneration was produced in the livers of all the animals; a hyaline degeneration in the myocardium of one case (17) and in the islands of Langerhans of the pancreas in one case (16), while no such degeneration occurred in spleen and adrenals of any of the cases, but did occur in the kidneys of one case (18), in the myocardium of three cases (16, 18 and 19), in the lungs of three cases (16, 17 and 18), and in the pancreas of three cases (17, 18 and 19).

Summarizing the foregoing results, the intravenous injection of pancreatin, trypsin and amylopsin could produce a hyalin-like and an amyloid-like degeneration in the bone marrow, liver, kidneys, spleen and myocardium of most of the cases and also in the blood vessels and pancreas in a few cases.

The reason I call the substance stained a slight reddish violet with Pianese's solution and gentian-violet an "amyloid-like" substance is that if the amyloid-like degeneration is a hyaline degeneration, the degenerated cells or tissues should be stained a brick red, because Pianese's solution gives a characteristic color to each substance; that is, a brick red to hyalin, a bright green to colloid and a dark reddish violet to a substance resembling amyloid. If this change is an amyloid degeneration, those cells and tissues should be stained a red color with gentian-violet, whereas they have been stained a dark reddish violet or a slight reddish violet with Pianese's solution. Therefore it should be described as an intermediate degeneration between hyaline and amyloid degeneration, or rather an "amyloid-like" degeneration.

At present, however, we have no sufficient knowledge of the chemistry of amyloid and hyalin or colloid, although von Recklinghausen regards them as representing but different stages in the evolution of the same body.

Their differentiation by staining reactions at present, therefore, is not fully characteristic or always as satisfactory as Davidsohn,¹⁹ Krakow¹⁸ and Maximow²⁰ have believed, for they are closely allied bodies; however, Pianese²⁷ has recently differentiated these materials with his staining solution, which is the only method available at present.

Thus the amyloid-like degeneration produced in my experiments probably is an early stage of amyloid degeneration, and therefore the hyalin-like substance should be a precursor of amyloid, as Lubarsch²⁸ has suggested.

Considering the facts, amyloid probably passes through a hyaline stage in its formation, and these hyalin-like and amyloid-like substances seem to me likewise to be products of cell degeneration.

F. ON THE PRODUCTION OF ARTERIOSCLEROSIS IN RABBITS BY THE INJECTION OF PANCREATIN, TRYPSIN AND AMYLOPSIN

Up to the present we have had many investigations and observations on the production of experimental arteriosclerosis by the injection of extracts of vegetable and animal substances, bacteria and bacterial toxins, etc., or feeding with animal substances and lipoids, and also by various mechanisms. I could, however, find no reports on the production of arteriosclerosis by ferments. I produced arteriosclerosis in the rabbits by the repeated injection of pancreatin, trypsin and amylopsin. In the foregoing experiments there were presented thickening of the intima together with an increase of the media of the smaller or medium sized pulmonary arteries in four cases (5, 11, 24 and 25) in twelve rabbits injected with pancreatin; in two cases (20 and 21) of three rabbits injected with trypsin, in the smaller or medium-sized pulmonary, hepatic and splenic arteries in one case (16), of the renal and pulmonary arteries in one case (17), and also of the pulmonary arteries in one case (18) of four rabbits injected with amylopsin. These rabbits were repeatedly injected into the ear veins with the antigens. Unfortunately, I did not examine at necropsy the larger arteries of these rabbits. In these cases, no fatty degeneration was recognized in the lesion of the intima.

Jores,²⁹ in 1903, asserted concerning the development of arteriosclerosis that fatty degeneration of the thickened intima is an impor-

27. Pianese: Mallory and Wright's Pathological Technique, Ed. 6, 1915, p. 412.

28. Lubarsch: Centralbl. f. allg. Path. u. path. Anat. **21**: 1910, No. 3.

29. Jores: Wesen und Entwicklung der Arteriosklerose, Wiesbaden, 1903.

tant factor for the determination of arteriosclerosis, but Torhorst,³⁰ in 1904, observed that arteriosclerosis of the pulmonary arteries showed no fatty degeneration in the intima. According to Tawara's¹² assertion on this subject (which was further studied by him in 1913), a thickened intima which shows no fatty degeneration is also arteriosclerosis.

Tawara's assertion, therefore, suggested to me that the thickening of the intima and some of the media, without fatty degeneration, of the smaller or medium pulmonary, hepatic, renal and splenic arteries in my experiments should certainly be considered as arteriosclerosis; the thickening of the intima would be the stage of arteriosclerosis corresponding to Jore's²⁹ hyperplastic intima thickening, or to Kon's³¹ second type, even if there were no fatty degeneration; however, there would appear to be a fatty degeneration following degenerative processes in the intima.

The essential conditions for the production of arteriosclerosis are not determined at present, and I should not dare to assume that they are determined by my experiments; but I venture the opinion that the arteriosclerosis produced in the experiments recorded here was due to pancreatin, trypsin and amylopsin acting on the intima of the vessel walls as a poison, with resulting hypertension, subacute or chronic progressive changes in the interstitial connective tissues and subsequent retrogressive changes in the parenchymatous cells, especially of the liver and kidneys. On the production of the arteriosclerosis in rabbits, however, one would have a question, because normal rabbits have sometimes a spontaneous arteriosclerosis, a condition which was investigated by Bennecke,³² who found arteriosclerosis in twelve out of 400 apparently normal rabbits. In 1908 Kon³¹ found it in one normal rabbit during his researches on experimental arteriosclerosis. Other workers have also described the condition.

I cannot, however, believe that the arteriosclerosis produced in my experiment is a spontaneous arteriosclerosis, because it was produced in about 33 per cent. of the animals (four out of twelve rabbits) with pancreatin, in about 66 per cent. (two of three rabbits) with trypsin, and in 75 per cent. (three out of four rabbits) with amylopsin. I could find no spontaneous arteriosclerosis in fifty-three rabbits killed within three days after one injection of pancreatin, nor in nine normal rabbits employed in the foregoing experiments. Loeb³³ also could not find spontaneous arteriosclerosis in 280 apparently normal rabbits;

30. Torhorst: Beitr. z. path. Anat. u. z. allg. Path. **36**: 1904.

31. Kon: Verhandl. d. Jap. path. Gesellsch. **3**: 1913.

32. Bennecke: Virchows Arch. f. path. Anat. **191**: 1908, Part 2.

33. Loeb, O.: From Bennecke's article in Virchows Arch. f. path. Anat. **191**: 1908, Part 2.

therefore, I conclude that the arteriosclerosis found in my experiments is an artificial arteriosclerosis, but not spontaneous.

G. SUMMARY AND CONCLUSIONS

1. In rabbits, when introduced into the blood stream, both native and alcoholic pancreatin give rise to toxicity, such as trembling, uneasiness, difficulty in walking, dyspnea, and strong palpitation of the heart, and sometimes to shock a short time after the injection; however, the alcoholic extract is much less toxic than the native, but the toxicity of the latter decreases after the promotion of immune processes in the body.

2. Sometimes an acute inflammation, followed by abscess or gangrene is produced by subcutaneous injections.

3. A dose 0.05 gm. of native pancreatin to 1 kg. of body weight seems to be the minimal lethal dose in rabbits injected intravenously.

4. Both native and alcoholic pancreatin produce hyperemia, hemorrhage and thrombosis throughout the bodies of rabbits injected once, and sometimes make the blood incoagulable.

5. Fat infiltration was found in the livers of some rabbits killed within three days after one injection.

6. Some rabbits injected with pancreatin developed a crippled condition in the legs during immunization, which was due to amyloid degeneration of the bone marrow.

7. Some enlargement of the spleen and adrenals and amyloid degeneration of the bone marrow in most cases, and also jaundice in one case immunized with pancreatin, were found at necropsy.

8. Immunized rabbits in general showed some hyperplasia in the interstitial tissues of the liver, kidneys, spleen, lung, myocardium, bone marrow and pancreas, especially a subacute interstitial and parenchymatous hepatitis and nephritis in most cases, some necrosis of the bone marrow in the majority of cases, and an increase of phagocytic and giant cells in the spleen in all the cases. The rabbits also showed amyloid degeneration in the bone marrow, an amyloid-like and a hyaline degeneration in the liver, kidneys, spleen and myocardium in the majority of cases, and also fatty degeneration in the liver, kidneys, spleen and myocardium in all the cases; an arteriosclerosis of the smaller or medium pulmonary arteries in four cases, and a hyaline degeneration of the portal vein in one case out of twelve.

9. Trypsin and amylopsin give rise to the same toxicity and pathologic changes as pancreatin.

10. Rabbits immunized with trypsin developed an amyloid-like degeneration in the liver, kidneys, spleen and bone marrow, but a hyaline degeneration in the myocardium, an arteriosclerosis in the

smaller or medium pulmonary arteries, a fatty degeneration in the liver, kidneys, spleen and myocardium in the majority of cases, some enlargement of spleen and kidneys in most cases and a jaundice in one case.

11. Rabbits immunized with amylopsin showed an amyloid degeneration in the bone marrow, an amyloid-like degeneration in the liver, in the kidneys of most cases, and in the media of the medium-sized pulmonary arteries in one case; a hyaline degeneration in the myocardium and pancreas, one case of each, and an arteriosclerosis of the smaller or medium pulmonary, hepatic, splenic and renal arteries in a few cases; also a fatty degeneration in the liver, spleen and myocardium of most of the other cases.

I wish to express my sincere thanks to Prof. P. Kyes for his interest and many helpful suggestions.

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THE STANDARDIZATION OF ANTIPNEUMOCOCCUS AND ANTIMENINGOCOCCUS SERUMS *

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During the latter part of 1916 the laboratory received reports indicating that some of the commercial antipneumococcus and antimeningococcus serums which had been purchased in the state lacked potency when used in the treatment of cases of pneumonia and meningitis.

Specific regulations for the standardization of diphtheria antitoxin were prescribed by an act of Congress in 1903, and following this, in 1907, the immunity unit for measuring the strength of tetanus antitoxin was officially defined and the method of standardization published. Since that time, and especially during the last four or five years, while the production of different immune serums such as are produced by immunization with the pneumococcus, streptococcus, meningococcus and the dysentery bacillus has been greatly extended, no federal regulations establishing standards of potency have been formulated for these serums. The federal license to sell these serums has been issued solely on the basis of an inspection of the manufacturer's plant and tests of the purity of the serums. No tests of the potency of the serums were made until the last few months of 1918, and no standards of potency have yet been formulated or established.

Ever since the summer of 1915 this laboratory has produced antipneumococcus serum, and was therefore fully equipped to test samples of this serum which were purchased; but it was only in July, 1916, that the laboratory undertook the production of antimeningococcus serum, so that careful studies were necessary in order to acquire the technic necessary to develop methods which could become accept-

* From the Division of Laboratories and Research, New York State Department of Health.

able standards. The results of these tests of the serums produced by different laboratories, and our experience in formulating standard methods for the state are considered of sufficient interest to record, despite the fact that none of the methods by which these serums can be tested is wholly satisfactory or comparable to those used in testing the antitoxins of diphtheria and tetanus.

ANTIPNEUMOCOCCUS SERUM

Early Protection Tests of Antipneumococcus Serum.—While protection tests were early recognized as affording the most satisfactory means of testing the potency of pneumococcus immune serum, confusion was for some time caused by the irregular and conflicting results obtained by different workers due, as we now know, in a large measure to their more or less indiscriminate use of organisms belonging to the homologous or heterologous groups. To Neufeld chiefly is due the recognition of this source of error, and the present methods on which are based the standardization of antipneumococcus serum. He first classified as irregular strains, all those which did not correspond with the culture which had been used extensively by him, and which he designated as typical. Later he recognized at least three other types and, owing to the frequent occurrence of these atypical strains, he laid great emphasis on the importance of identifying each culture by serologic tests.

Cole and his co-workers at the Rockefeller Hospital have since, by their classification of the pneumococcus, developed a working procedure of great practical value in the standardization of serum as well as in the rapid diagnosis of types.

Neufeld, Römer, Wadsworth, Washburn and others in testing the potency of immune serum used rabbits extensively. These were generally given intravenous injections of immune serum followed, after an interval, by injections of homologous culture. Or, in other instances, the injection of live organisms preceded that of the serum (Wadsworth). It was found, however, that the longest period between the injections of a virulent culture and the effective administration of the serum was approximately four hours.

Six years ago the results of studies of the action of immune serum in the treatment of pneumococcus infection of the rabbit were published (Wadsworth) which demonstrated that the true therapeutic value of such serums should be determined not by their protective action, but by their curative action when given after pneumococcus infection had developed. Distinctions were then drawn between

the parasitism¹ of the agent and its toxin production. The action of immune serum was found to be very largely limited to neutralization of the toxins or poisons. The destruction of the pneumococci in the lesions whether partial or complete was secondary.

In order to demonstrate experimentally beyond question the therapeutic value of the serum, this method of testing was essential; but as a basis for the standard method of testing the degrees of potency in different antipneumococcus serums with the necessary precision, it is far from practical now that the therapeutic value of a high protective titer is so well established.

As early as 1909 Neufeld developed what he considered a satisfactory method for the standardization of serums, using mice weighing between 18 and 20 gm. instead of rabbits. He injected subcutaneously or intravenously 0.2 c.c. of the serum to be tested, followed after an interval of two or three hours by varying amounts of a twenty-four hour broth culture given intraperitoneally. He originally held that the mice should survive at least from seven to ten days, but later reduced the time to three or four days, and in his later tables recorded results only up to the forty-eighth hour. He recorded that satisfactory protection could be obtained against 0.1 c.c., and even against 0.2 c.c. of culture, but emphasized the importance of having the culture of high virulence. Neufeld also suggested that the culture and serum might be given simultaneously, and that a standard serum of known potency might be used as a control.

Results of repeated agglutination tests made at this laboratory had early shown that the relationship between the protective and the agglutinative titers were inconstant at times. While the agglutinative titer may be high during the early months of immunization, a gradual decline may and frequently does occur, while the protective titer remains stationary or even advances.

When the work was first begun in our laboratory a careful study was made of the different methods of determining the protective titer of immune serum in the hope of gaining greater precision in demonstrating slight differences in the therapeutic potency. Numerous

1. Parasitic activities of the pneumococcus are the disturbing elements not only in determining the action of the serum therapeutically, but in determining the potency of the serum by protection tests. It is difficult to conceive of any fundamental difference existing in the pneumococcus poisons except quantitatively in the different cultures. The parasitic activities, however, vary greatly in degree, constituting the chief variable factor and one which it is extremely difficult to control. The differentiation of the organisms of the different types is based entirely on differences in the bacterial cell, and has not yet been demonstrated to comprise also qualitative differences in the pneumococcus poisons or toxins; in fact, the differences in the therapeutic, and possibly the protective action of homologous and heterologous serums might conceivably be attributed to differences in parasitic activity of the organisms.

changes in the method were tried. A standard dose of the culture containing a relatively small number of fatal doses and varying amounts of serum in corresponding greater dilutions, and then smaller quantities of serum as a standard dose, were all tested in a series of preliminary investigations which, however, were sufficiently complete to warrant the conclusion that further and prolonged study and practical experience with any new methods would be necessary before they could be adopted. Although these investigations have not yet been completed, the only important change in the methods as they have been used at the Rockefeller Hospital that gave greater precision in the test was the use of 0.1 c.c. of serum instead of 0.2 c.c.; 0.1 c.c. of the serum having frequently protected against as large a dose of the culture as 0.2 c.c., showing that when the larger dose was used an excess of serum was present. This accounts for the fact that 0.1 c.c. of serum instead of 0.2 c.c. was used in many of the tests where the doses of standard culture ranged from 0.1 c.c. to 0.5 and even 0.6 c.c.

Antipneumococcus serums which were produced by different laboratories were obtained, and the protective potency of all of them was tested. The results of all of these tests are recorded in Table 1. The laboratories are designated by letters, and the letters which have been used correspond to those which were used by Amoss to designate the same laboratories in his tests of the antimeningococcus serums.

As compared with the serums of laboratories G and H, those of Laboratories C, E and F, with one exception, were all so far below standard as to fail to show protective value with the small dose of culture which was used in the test. The one exception was the second sample of serum produced by Laboratory E. The first serum of this laboratory had, however, previously failed in the test. The laboratory was notified at that time and immediately took precautions to send for cultures and protocols of our methods; they had no difficulty in producing a satisfactory serum by the time the second sample of serum was examined. The serums of Laboratories G and H of this table, and Laboratory B not listed in the table, maintained uniformly in these and other tests a high degree of potency. These laboratories were all research laboratories not primarily engaged in manufacture for sale. The serums of Laboratories C, E and F were all commercial serums purchased in the open market. Although licensed to sell, not one of these commercial laboratories produced a satisfactory Type I serum until their attention was directed to their shortcomings.

Thus, as a direct result of these potency tests of commercial antipneumococcus and antimeningococcus serums offered for sale in the State of New York, and also following reports that certain commercial serums lacked therapeutic value, the Commissioner of Health,

feeling considerable responsibility in the matter, called the attention of the Public Health Council of the state to the situation. The council acted promptly, passing the following regulation of the Sanitary Code:

CHAPTER IX. Regulation 1. Sale of antipneumococcus and antimeningococcus serum regulated. No serum for the treatment of pneumonia or of meningitis shall be sold or offered for sale in the State of New York unless each package is accompanied by a label or circular on which is stated the potency of the serum as tested by the methods established by the rules and regulations of the state commissioner of health; and no such serum shall be sold or offered for sale the potency of which does not equal or exceed the minimum fixed in such rules or regulations.

This regulation will become effective February 15, 1918.

TABLE 1.—THE RESULTS OF TESTS OF THE POTENCY OF ANTIPNEUMOCOCCUS SERUM PREPARED IN DIFFERENT LABORATORIES

TITER OF PROTECTION TESTS IN MICE

Control Mice: Culture without serum 0.000001 c.e. killed mice in less than forty-eight hours.
Cultures: 18 hour Witte peptone broth cultures made from recent semisolid stock cultures.

Laboratory	Date Tested	Type I Neutral Culture Homologous Culture of Serum Produced by Laboratory H		Type I R. D. Culture Heterogenous Culture of Serum Produced by Laboratory H		Remarks
		Quantities	Protection	Quantities	Protection	
H	3/29/16	0.1 serum 0.5 culture	+	Not tested	..	Serum clear
G	3/29/16	0.1 serum 0.5 culture	+	Not tested	..	Serum clear
E	1/10/17	0.2 serum 0.1 culture	0	Not tested	..	Serum clear
H	1/10/17	0.1 serum 0.3 culture*	+	Not tested	..	Serum clear
H	8/1/17	0.1 serum 0.6 culture	+	0.2 serum 0.2 culture	+	Serum clear
H	9/13/17	0.1 serum 0.4 culture	+	0.2 serum 0.1 culture	+	Serum clear
C	9/13/17	0.1 serum 0.2 culture	0	0.2 serum 0.1 culture	0	Serum slightly turbid; sterile upon tests
E	9/25/17 and 10/3/17	0.1 serum 0.3 culture	+	0.2 serum 0.1 culture	+	Serum very turbid; hemolytic; sterile upon tests
F	9/25/17	0.1 serum 0.1 culture	0	0.2 serum 0.1 culture	0	Serum slightly turbid; hemolytic; sterile upon tests
H	9/25/17	0.1 serum 0.5 culture	+	0.2 serum 0.2 culture	+	Serum clear

* Made as a control, therefore, not tested above 0.3 culture; for upper limits of potency see other tests.

This, we believe, is the first time a state has prescribed and made effective regulations for testing biologic products which are offered for sale.

RULES AND REGULATIONS FOR THE TESTING OF THE POTENCY OF
ANTIPNEUMOCOCCUS SERUM²

I. Type of Serum.—Antipneumococcus serum for the treatment of pneumonia which is offered for sale in the State of New York shall be prepared by the immunization of animals against pneumococcus of Type I.

II. Minimum Standard of Potency.—The potency of the antipneumococcus serum intended for therapeutic use shall equal that of the standard serum prepared by the Laboratory of the State Department of Health and which is supplied on request. The standard serum is of such potency that under the conditions prescribed, 0.2 c.c. will protect a mouse 16 to 22 grams in weight for at least 4 days against at least 0.1 c.c. of the standard culture of pneumococcus Type I, 0.000001 c.c. of which will kill the control mouse in less than 48 hours.

III. Standard Cultures.—The standard culture of pneumococcus Type I employed for testing purposes may be obtained from the Laboratory of the State Department of Health. However, before the protection tests are performed, the virulence of the culture shall be determined by experiment to be such that 0.000001 c.c. of an 18-hour broth culture will kill a mouse of 18 to 22 grams weight within 48 hours.

IV. Method of Testing the Potency of the Serum.—The dilution of the culture and of the serum shall be made in broth and prepared immediately before the test is performed and in such manner that no less than 0.5 c.c. are measured. Thus 2 c.c. of the serum are diluted with 3 c.c. of the broth, so that 0.5 c.c. of the mixture will contain 0.2 c.c. of the serum. Similarly 1 c.c. of the culture is added to 4 c.c. of the broth, so that 0.5 c.c. of the mixture will contain 0.1 c.c. of the culture.

In making the injection 0.5 c.c. of the diluted culture and 0.5 c.c. of the diluted serum are thoroughly mixed in the barrel of the syringe and in two minutes injected into the peritoneum of a mouse weighing from 16 to 22 grams. Moreover, control tests with standard serum and control tests of the virulence of the culture without the serum are made at the same time. The protective titer of the serum against the culture is the potency and should be regarded as equal or in excess of the standard serum.

V. Physical Properties.—The serum shall be free from all the cellular or solid elements of the blood. In order to facilitate inspection, the serum should be put up in containers of colorless transparent glass.

VI. Sterility of the Serum.—Sterility tests of the final product shall comply with the requirements of the U. S. Public Health Service.

VII. Expiration Date.—Expiration date for the sale of the serum shall comply with the requirements of the U. S. Public Health Service.

ANTIMENINGOCOCCUS SERUM

A similar investigation was also made of the antimeningococcus serums which were produced by these different laboratories. Before this was completed Amoss tested independently serums produced by all of these laboratories, using in these tests practically similar methods, but Amoss used only selected strains publishing the results he obtained from five standard cultures of the meningococcus, whereas a much larger number of strains were used in the production of each of the serums, and it might well have happened that some of the strains were not used in the immunization of the horses at the time the serum was taken from them. It was thought that the results of the tests of all the strains used in the immunization of our horses would afford a safer basis of comparison.

2. These rules and regulations are subject to revision from time to time.

The testing of the potency of antimeningococcus serums has always been a difficult problem owing to the unsatisfactory results of protection tests, and the difference of opinion as to the therapeutic value of other antibodies which may be present in the serum.

Kraus and Doerr used bacterial extracts that were toxic for guinea-pigs and attempted to test the protective value of serums against them, but their results were not constant owing to both the variability in the toxicity of the extracts and the resistance of the different pigs.

Many workers have attempted to use live cultures for protection tests. Under the direction of Park a large series of tests were made, but a minimum lethal dose for guinea-pigs could not be determined, as there was so much variation in the reaction of the different pigs in a series. Flexner and Amoss obtained better results by using small pigs weighing from 90 to 100 gm.; but even with these, variations in resistance were met with. Hitchens reports fairly constant results if very young cultures are suspended in dilute guinea-pig serum and white mice used in making the protection tests. The practical value of his method, however, has not yet been established.

The other antibodies in the serum have been studied by a large group of workers. Among them, Neufeld investigated the bacteriotropic substances, Hohn the bacteriolytic, and Kolle and Wassermann the bacteriotropic, antitoxic, agglutinating, and complement fixing properties. Neufeld, Krumbein and Schatloff, Baecher, and Hachla concluded that the complement fixing, agglutinating, and *opsonic* substances in the serums did not run parallel. Kolle and his helpers did not find the complement fixing and the bacteriocidal properties present in equal amounts. Later workers, however, have not confirmed these results. Amoss and Wollstein determined that the *opsonic*, complement fixing and agglutinating properties of a serum ran parallel. They tested the serums from their horses by all three of these methods until this was determined. They then relied wholly on the agglutination test to determine the value of the serums.

Amoss reported that the statistics which he had been able to gather from the use of the serums distributed from the Rockefeller Institute indicated that the serums which possessed a high agglutinating titer gave excellent therapeutic results, and that frequently when complaints had been received regarding the failure of the serums to give satisfactory results in the treatment of cases the serum did not possess high agglutinating titer. Such reports as we have received are also to this effect.

Attempts to formulate protective tests with the meningococcus having not as yet come into general use, it has been necessary to use either the agglutinating or complement fixing properties of the serum,

tion method. Although agglutination and complement fixation are both used, few, if any, laboratories have sufficient confidence to rely on complement fixation alone without some control by agglutination against the different strains of the meningococcus which are used in the immunization of horses.

Although many important technical changes have been introduced in our methods of determining the agglutinating titer of antimeningococcus serums since the tests of the commercial serums were made,

—ANTIMENINGOCOCCUS SERUMS PREPARED IN DIFFERENT LABORATORIES

Agglutination Titer at 55 C.																									
Stock Cultures																							Appearance		
61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83			84
0	0	0	0	10	0	0	0	0	0	0	0	10	10	0	0	0	0	0	0	0				Amber colored; slightly cloudy (Sept. 1917)
0	10	200	100	200	200	100	100	50	200	10	50	500	100	200	50	100	50	50	10					
100	10	800	10	800	500	100	100	10	800	100	100	10	200	100	10	50	10	50	10	10	10	...	100	Amber colored; very cloudy (Sept. 1917)
10	10	100	50	50	10	50	10	50	10	10	10	200	10	50	10	10	10	10	10	10	
10	0	10+	50	10	50	10+	100	0	200	50	200	0	200	200	200	0	0	200	0	100	0	200			Amber colored; slightly cloudy (Sept. 1917)
50	100	500	100	200	200	100	200	200	200	500	100	200	500	200	100	200	100	100	200	
100	50	800	200	800	800	100	200	100	800	800	800	800	800	800	800	500	800	800	800	10	200	...	10	Amber colored; slightly cloudy (Sept. 1917)
0	10	50	10	50	10	...	50	10	200	...	10	100	200	50	10	50	50	10	0	Amber colored; slightly cloudy (Sept. 1917)	
50	100	50	10	800	50	100	50	0	800	10	200	200	800	200	800	800	800	800	100	10	...	10		Straw colored; clear (Aug. 1917)
10	100	200	200	200	200	100	200	500	200	100	200	200	200	200	...	200	100	200	Straw colored; clear (Aug. 1917)	
500	500	800	200	200	800	800	200	200	100	200	200	200	200	500	500	200	800	...	200	500	200	...	100		
200	200	500	500	100	800	200	100	200	800	200	100	100	...	100	100	100	100	...	100	100	100				
0	10	50	10	100	50	...	10	10	200	10	50	200	200	50	100	200	50	50	10					
Agglutination Titer at 38 C.																									
0	0	0	0	0	0	10	0	0	0	0	0	0	0	0	0	0	...	0	0	0			
10	10	0	50	10	50	50	50	10	10	50	10	10	50	10	100	...	10	10	10				
0	50	0	10	50	50	200	100	50	50	10	10	50	100	50	200	...	50	10	50				
0	50	50	50	200	100	500	200	200	50	100	100	100	200	200	500	...	100	50	100				
10	50	50	50	500	100	50	200	100	100	200	200	50	200	100	200	...	500	50	50				

Agglutination Titer at 38 C.

0	0	0	0	0	0	10	0	0	0	0	0	0	0	0	0	...	0	0	0	
10	10	0	50	10	50	50	50	10	10	50	10	10	50	10	100	...	10	10	10	
0	50	0	10	50	50	200	100	50	50	10	10	50	100	50	200	...	50	10	50	
0	50	50	50	200	100	500	200	200	50	100	100	100	200	200	500	...	100	50	100	
10	50	50	50	500	100	50	200	100	100	200	200	50	200	100	200	...	500	50	50	

the methods which were used in these tests correspond closely with those which were used by Amoss of the Rockefeller Institute when he tested the commercial serums of these same laboratories against five standard cultures of the meningococcus.

In Table 2 is recorded the agglutinating titer of all of these serums with practically all of the cultures which were used in this laboratory. The laboratories are designated by letters which correspond to the letters which were used by Amoss to designate the same laboratories.

It is evident from these results that the agglutination of the different cultures and the agglutinating action of the different serums on

the same culture as well as on the different cultures, vary greatly, and that in the absence of any standard set of cultures representative of the different types or groups of the meningococcus, and in the absence of any standard serum or standard methods with which to make the tests of potency, it was necessary to test the serums with all of the strains which were used in immunizing the horses. Although the results of our tests confirm the general conclusions of Amoss, one or two of the serums might be credited with a higher potency than they actually possessed if results from any five of the cultures were selected as a basis for comparison. This is especially noteworthy on account of errors in the classification of strains as normal, irregular, or parameningococci. In fact, the classification of a few of the strains which were used in our tests according to this grouping have since been found to be faulty. Some of the variation in the action of the serums was attributed to the fact that when such a large number of strains were used in immunizing the horses, the amount of culture taken from each of them for the inoculation was varied from time to time, one strain giving greater reactions in the smaller doses than another strain. It was necessary to increase or diminish the dose as the agglutinating titer rose or fell. This procedure becomes increasingly complicated when cultures which fail to react with the polyvalent serum are continually added to the set of cultures which is used for immunizing the horses, but in the light of the results previously tabulated showing such marked variation in the agglutination with different cultures of the homologous group, it is apparently necessary and for the present indispensable to continue this practice. We now have an experiment under way testing the effect of immunization with but four strains selected as representative of the different groups of the meningococcus, and it is possible that with these four cultures a polyvalent serum will be obtained which will possess sufficient potency when tested with many if not all of the strains of the different groups.

On the basis of these tests of the antimeningococcus serums, the commercial and noncommercial laboratories are not quite so strikingly differentiated as compared with the results of the tests of antipneumococcus serums. Laboratories B, G and H are research laboratories, and have usually been found to produce serum of fairly uniform and satisfactory potency, but in the table the serum of Laboratory B in this instance was an exception. Laboratories A, C, D, E, F and I are commercial laboratories. The serums which they produced were far from uniform, excepting those of Laboratory A which were in both instances no more potent than normal horse serum. The first serum of Laboratory E, September, 1916, as compared with the second, September, 1917, shows striking differences in potency. The same is true of

the two serums of Laboratory F. When the first tests of this table were completed, it was considered necessary to direct the attention of Laboratories A, C, D, E, F and I to the fact that their serums lacked potency by this method of testing, and this may account for the improvement in some of the serums.

It is thus very evident that a uniform method of testing the potency of antimeningococcus serum should be adopted, but the problem of formulating a standard method which could be used by the different laboratories and give reliable results was not so simple with antimeningococcus serum as it was with antipneumococcus serum. Many technical difficulties were encountered. A method of preparing standard suspensions for the agglutination reaction had to be devised and tested. A standard serum to be used for purposes of comparison in all of the tests had to be selected, and finally, standard cultures had to be chosen, and all of this without delay.

The staff of the British Army working under Gordon have differentiated four types — Type I corresponding to the Rockefeller parameningococcus, Type II corresponding to the normal or regular group, and Types III and IV are included in the Rockefeller irregular group. Gordon and those who have been able to confirm his results consider this classification complete with all of the strains of the meningococcus which they have been able to isolate and classify by both agglutination and absorption tests.

Other British research workers under the direction of F. W. Andrewes serving the civil population, agree more closely with the American grouping. They reached the conclusion that there are two main groups, (1) including the Gordon Types I and III, and (2) corresponding to the Gordon Types II and IV. These two main groups can be further divided into subgroups.³

For the present, in our work the American classification has been adopted because certainly two groups can be definitely recognized if all of the strains which fail to correspond in their reactions with these two groups are classified as irregular or atypical strains.

In choosing the four standard cultures representative of the different types of the meningococcus, it was decided to take one culture from the normal, one from the para, and two from the irregular strains; but the first task was to test all of the strains against monovalent serums by the agglutination and absorption tests in order to be certain of their identity and classification. The monovalent rabbit

3. There is a discrepancy in the use of the terms "para" and "normal" in the classification of meningococci. The workers at the Rockefeller Institute apply the term "para" to organisms belonging to the Gordon Type I, and the term "normal" to those in the Gordon Type II; while workers in England and France refer to organisms belonging to the Gordon Types II and IV as "para."

serums were prepared in the laboratory from selected strains, the identity of which had been determined beyond dispute, and in addition to these serums standard English serums and bacterial suspensions were obtained from the Medical Research Committee of London. Some of the serums had been prepared in July, 1917, and were not used until January, 1918, and gave very weak reactions with the bacterial suspensions that had been sent with them from England. Many of the stock meningococcus cultures failed to agglutinate well with the English serums. Some, however, were found to agglutinate with the different types. Many of the cultures that agglutinate with Type III serum gave weak reactions with Type IV serum also. The cultures that gave reactions with the English monovalent type serum were then tested with the polyvalent horse serum to determine if they were agglutinated in dilutions of 1 to 800 or more.

Amoss at the Rockefeller Institute had been using Nos. 1, 7, 10, 30 and 60 in testing commercial serums, and Colonel Whitmore in Washington, D. C., was using Nos. 1, 10, 30 and 60 in the preparation of vaccines. It seemed, therefore, advisable to use as many of these cultures as possible for standards. Culture 1, classed in this country as normal, and by the British Army as Type II, did not agglutinate in the polyvalent horse serum diluted 1 to 800 (and also failed to develop monovalent serums of high potency in the rabbit), so another culture belonging to this group had to be chosen. No. 46 was found to fulfill the requirements. No. 10 and No. 30 were chosen as representative of the irregular group. No. 60 was chosen as representative of the para or British Army Type I. All of these cultures gave a high agglutinating titer in the polyvalent horse serums, and in the rabbits produced monovalent serums of high titer.

Absorption tests were made before these cultures were finally chosen. Monovalent rabbit serums had been prepared against several cultures. Serum "A" against Culture 1, a normal strain. This serum diluted 1 to 400 agglutinated British Army Type II suspension; and diluted 1 to 100 British Army Type IV suspension. Serum "B" against Culture 30, an irregular strain, diluted 1 to 400 agglutinated British Army Type III suspension; diluted 1 to 300 agglutinated British Army Type IV suspension, and diluted 1 to 100 agglutinated British Army Type I suspension. Serum "C" against Culture 60, a para strain, diluted 1 to 300 agglutinated British Army Type I suspension. These three serums represent the three groups as classified in this country. Culture 46 absorbed the agglutinin from the monovalent normal serum "A"; Cultures 10 and 30 absorbed the agglutinin from the irregular serum "B," and Culture 60 absorbed the agglutinin from the para serum "C."

The cultures used for these agglutination and absorption tests were then plated, colonies picked and replated. The fishings from these last plates were then tested against the monovalent and polyvalent serums to prove that their reactions were the same as the original cultures. Then these subcultures were used for the standard strains to be sent to the manufacturers.

As a result of this work the following rules and regulations were drawn up with the advice and counsel of members of the consulting staff of the State Department of Health and the Public Health Council. They were then submitted to the Commissioner of Health for his approval.

RULES AND REGULATIONS FOR THE TESTING OF THE POTENCY OF ANTI-MENINGOCOCCUS SERUM⁴

I. Type of Serum.—Antimeningococcus serum for the treatment of meningitis which is offered for sale in the State of New York shall be prepared by the immunization of animals against at least four standard cultures representative of the principal types of the meningococcus.

II. Minimum Standard of Potency.—The potency of antimeningococcus serum intended for therapeutic use, when tested and compared with the standard serum supplied on request by the Laboratory of the New York State Department of Health, shall have an agglutinative action in a dilution of 1 to 800 with at least the four representatives of the principal types of meningococcus, under conditions in which a standard suspension is employed and the tubes maintained for 16 to 24 hours at 55 C.

III. Standard Cultures.—The standard cultures of meningococcus representative of the principal types may be obtained from the Laboratory of the State Department of Health. They are cultures which have been identified by serological tests and which possess distinctive agglutinative and antigenic properties.

IV. Standard Suspensions.—The standard suspensions for performing the agglutinating tests are so prepared as to correspond in opacity with a standard suspension of barium sulphate containing 3 c.c. of a 1 per cent. barium chlorid solution in 97 c.c. of a 1 per cent. sulphuric acid solution. Such a standard meningococcus suspension contains approximately 2,000 million cocci per cubic centimeter.

V. Method of Testing the Potency of the Serum.—Normal saline solution (0.85 per cent.) should be used as the diluent. After dilution with the serum the final mixture should contain 1,000 million cocci. The standard culture suspensions should be added in agglutination tubes (8 to 10 mm. in diameter), to the diluted serums to be tested, and also similar dilutions of the standard serum. These test mixtures should be incubated at 55 C. for from 16 to 24 hours. The titer thus determined is the maximum dilution of the serum in which definite clumping of the meningococcus in the suspension can be easily detected by the unaided eye. The agglutinative titer which is to be recorded is the potency of the serum.

VI. Physical Properties.—The serum shall be free from all the cellular or solid elements of the blood and should not contain traces of hemoglobin or bile which can be detected by the unaided eye. In order to facilitate inspection, the serum should be put up in containers of colorless transparent glass.

VII. Sterility Tests.—The sterility tests of the final product shall comply with the requirements of the United States Public Health Service.

VIII. Expiration Date.—Expiration date for the sale of the serum shall comply with the requirements of the United States Public Health Service.

4. These rules and regulations are subject to revision from time to time.

A CLINICAL STUDY OF MENINGITIS BASED ON TWO HUNDRED AND FIFTEEN CASES

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During the period Sept. 23, 1917, to July 15, 1918, there were admitted to the Medical Service of the U. S. Army Base Hospital, Fort Riley, 191 patients with meningococcic meningitis and twenty-four patients with meningitis due to other organisms. It is the purpose of this article to review the important diagnostic features presented by this series and to draw certain conclusions from the methods of treatment employed.

INCIDENCE

During the period, Sept. 23, 1917, to June 3, 1918, the date of admission of the last meningococcic meningitis patient, there were admitted to this hospital 24,406 patients. The incidence of meningococcic meningitis to all hospital admissions was, therefore, 0.77 per cent. These admissions were secured from Camp Funston, which housed the 89th and 92nd Divisions of the Army; the Medical Officers' Training Camp, and the Fort Riley Post. The largest number of patients with meningitis was from the recruits at Camp Funston. These recruits were drawn largely from the states of Kansas, Missouri, Nebraska, Colorado, South Dakota, New Mexico and Arizona. Kansas and Missouri have been regarded as endemic meningitis areas. As will be seen from Table 1, the largest number of patients with meningitis were from the states of Missouri and Kansas. Eighty-nine per cent. of all the patients with the disease were from rural districts. (See graphic Chart 1.)

The epidemic began late in September, 1917, and reached its height in November, gradually declining over the following six months. Table 2 shows the admissions by months for meningococcic meningitis. The mortality rate is also shown by months. In 191 cases the mortality was 28.8 per cent.

It will be observed in Table 3 that mixed infection occurred in thirteen instances with mortality of 92.3 per cent., while in Table 4 it will be seen that meningitis due to other infection than meningococcus occurred in eleven instances with mortality of 81.8 per cent.

TABLE 1.—MENINGOCOCCUS MENINGITIS EPIDEMIOLOGY BY STATES *

	Recovered		Deaths		Rural per Cent. Cases
	Urban	Rural	Urban	Rural	
Kansas.....	4	23	1	16	88.6
Missouri.....	11	38	0	19	83.8
Nebraska.....	1	15	0	2	94.4
Colorado.....	0	8	1	1	90.0
South Dakota.....	0	8	0	1	100.0
New Mexico.....	0	0	0	1	100.0
Arizona.....	0	1	1	1	66.0
Total.....	16	93	3	41	89.0

* The seven states listed in Table 1 supplied to a large extent the selective draft recruits of the Army, Camp Funston.

TABLE 2.—MENINGOCOCCUS MENINGITIS

Admissions	Recovery	Deaths	Mortality, per Cent.
September.....	1	1	50.0
October.....	10	6	37.5
November.....	43	29	40.0
December.....	30	7*	18.9
January.....	16	3	15.7
February.....	12	3	20.0
March.....	10	2	16.6
April.....	5	2	28.5
May.....	8	1	11.1
June.....	1†	1	50.0
Total.....	136	55	Aver. 28.8

* Including one case of lobar pneumonia.

† Clinically abortive type, no organisms found.

TABLE 3.—MORTALITY IN MENINGITIS DUE TO MIXED INFECTIONS

Date	Infection	Recovered	Deaths	Remarks
1917 Oct.	Streptococcus and meningococcus	1	1	
Nov.	Streptococcus and meningococcus	0	2	
	Streptococcus and pneumococcus	0	1	
	Pneumococcus and meningococcus	0	1	
Dec.	Streptococcus and meningococcus	0	1	
1918 Jan.	Streptococcus and meningococcus	0	1	Bilateral suppurative otitis media and parenchymatous nephritis
Feb.	Pneumococcus and meningococcus	0	1	
Mar.	Streptococcus and meningococcus	0	2	Both deaths followed postmastoid operation (Strept.) and meningococcus meningitis
May	Streptococcus and pneumococcus	0	2	
	Total.....	1	12	Mortality, 92.3 per Cent.

Meningitis

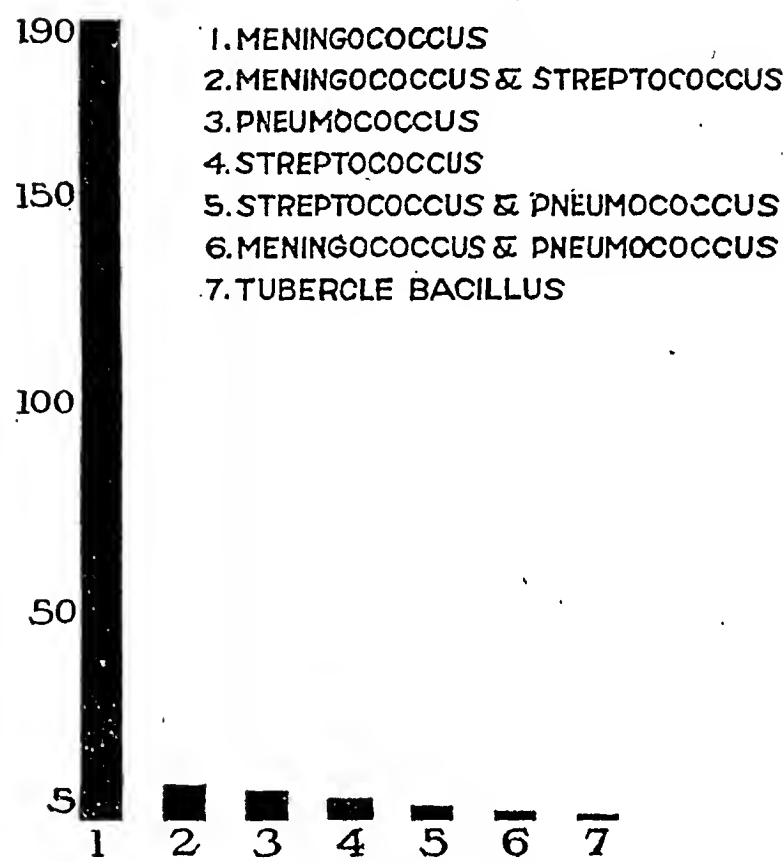


Chart 1.—Types of infection in meningitis.

TABLE 4.—MORTALITY IN MENINGITIS DUE TO OTHER INFECTIONS (NOT MENINGOCOCCUS)

Date	Infection	Recovered	Deaths	Remarks
1917				
Oct.	Pneumococcus.....	0	1	
Nov.	Streptococcus.....	0	1	
	Pneumococcus.....	2	0	
Dec.	Tubercle bacillus.....	0	1	
1918				
Jan.	Pneumococcus.....	0	1	Lobar pneumonia with pneumococcal meningitis
May	Streptococcus.....	0	2	Both deaths followed mastoidectomy and streptococcus meningitis
June	Streptococcus hemolyticus	0	1	Skull fracture followed by streptococcus meningitis
July	Pneumococcus.....	0	2	One death due to Type I pneumococcus meningitis during pneumonia; one death due to Type I pneumococcus meningitis and suppurative mastoiditis
	Total.....	2	9	Mortality, 81.8 per Cent.

TABLE 5.—RACE MORTALITY

	Cases Recovered	Fatal Cases	Total Cases	Mortality, per Cent.
Meningococcus:				
White.....	123	52	175	29.7
Colored.....	13	3	16	18.7
Mixed infections (Strept. and meningococcus):				
White.....	1	11	12	
Colored.....	0	1	1	
Other infections:				
White.....	2	9	11	
Colored.....	0	0	0	
All types meningitis:				
White.....			198	31.3
Colored.....			17	23.5

Total white, 198 or 92.1 per cent.; total colored, 17 or 7.9 per cent.; total, 215.

TABLE 6.—EPIDEMIOLOGY, CAMP FUNSTON, MENINGOCOCCUS MENINGITIS

	Recov- ered	Deaths	Mor- tality, per Cent.	Remarks
89th Division:				
354th Infantry.....	19	9	32.1	Includes one recovery from streptococcus and meningococcus meningitis; includes one death from streptococcus and meningococcus meningitis
356th Infantry.....	14	11	44.0	
353d Infantry.....	14	6	30.0	Includes one death from streptococcus and meningococcus meningitis
355th Infantry.....	10	3	23.0	
341st Field Artillery.....	7	0	0	
340th Machine Gun Bn.	4	2	33.3	Includes one death from streptococcus and meningococcus meningitis; includes one death from pneumococcus and meningococcus meningitis
314th Supply Train.....	0	1	100.0	
314th Engineers.....	3	2	40.0	
340th Field Artillery.....	3	2	40.0	
342d Field Artillery.....	1	3	75.0	
342d Machine Gun Bn.	2	2	50.0	
341st Machine Gun Bn.	3	0	0	
314th Sanitary Train.....	3	0	0	
314th Trench Mortar Bn. ...	1	1	50.0	Includes one death from streptococcus and meningococcus meningitis
314th Ammunition Train...	1	1	50.0	
314th Field Signal Bn.	2	0	0	
Quartermaster Corps.....	1	0	0	
Independent Organizations:				
164th Depot Brigade.....	19	10	38.0	Includes one death from streptococcus and meningococcus meningitis
323d Field Signal Bn.	0	1	100.0	Includes one death following mastoidectomy with streptococcus and meningococcus meningitis
529th Engineers Service Battalion (colored).....	2	0	0	
530th Engineers Service Battalion (colored).....	1	1	50.0	
Total.....	110	55	33.3*	
92d Division:†				
317th Ammunition Train...	3	1	25.0	
317th Supply Train.....	2	0	0	
317th Sanitary Train.....	2	0	0	
349th Machine Gun Bn.	1	1	50.0	
Total.....	8	2	20.0	

* Including six deaths mentioned due to mixed infections, streptococcus and meningococcus meningitis and one death due to pneumococcus and meningococcus meningitis.

† The 92d Division was made up of negro troops, largely from the Southern states. The command varied from approximately 12,000 (in October, 1917) to 15,000 men.

Ninety-two per cent. of the patients were white, while 8 per cent. were colored. In 175 white patients the mortality in meningococcus meningitis was 29.7 per cent.; among 16 colored patients the mortality was 18.7 per cent. The same difference in mortality will be noticed in meningitis due to all types of infection, shown in Table 5. For all types of meningitis among 198 white patients the mortality was 31.3 per cent., while among 17 colored patients the mortality was 23.5 per cent.

EPIDEMIOLOGY

The instances of meningitis arising at Camp Funston did not appear to arise from any particular endemic focus, but were more or less widespread throughout the various organizations.

In all, 175 cases were admitted to the hospital from Camp Funston; 13 cases were admitted from the Medical Officers' Training Camp at Fort Riley; 6 cases from the Fort Riley Post; 2 cases from the Base Hospital personnel; while 3 patients were civilians.

TABLE 7.—EPIDEMIOLOGY (MENINGOCOCCUS MENINGITIS) AT FORT RILEY

	Number Recovered	Number Deaths	Mortality, per Cent.
Medical Officers' Training Camp.....	10	3*	23.0
Post:			
311th Cavalry.....	0	1	100.0
13th Cavalry.....	0	1	100.0
40th Infantry.....	1	0	0
Mounted Service School.....	1	0	0
Quartermaster Corps.....	2	0	0
Total.....	4	2	33.3
Base Hospital:			
Medical Detachment.....	1	0	0
Army Nurse Corps.....	1	0	0
Total.....	2	0	0
Civilians.....	3	2	40.0

* Includes one death from postmastoid streptococcus (?) and meningococcus meningitis. Includes one death from postlobar pneumonia, pneumococcus and meningococcus meningitis.

TABLE 8.—AVERAGE STRENGTH OF COMMAND, 89TH DIVISION, CAMP FUNSTON, AND INCIDENCE BY MONTHS OF MENINGOCOCCUS MENINGITIS

	Strength of Command*	Incidence per 1,000
October.....	41,413	0.39
November.....	28,543	2.57
December.....	25,973	1.32
January.....	24,248	0.62
February.....	23,346	0.65
March.....	22,414	0.45
April.....	25,279	0.28
May.....	29,535	0.31
Average.....	27,594	0.82

* Based on weekly telegraph reports, Oct. 12, 1917 to June 7, 1918.

The strength of command 89th Division, Camp Funston, varied from approximately 41,000 men in October to 22,000 men in March. The strength of command, 92nd Division (Colored) Camp Funston, varied from 12,000 to 15,000 men. Table 8 shows the incidence of the disease per thousand by months. The highest incidence during the course of the epidemic was 2.57 per thousand for the 89th Division, and 0.26 per thousand for the 92nd Division.

TABLE 9.—APPROXIMATE STRENGTH OF COMMAND, 92D DIVISION, CAMP FUNSTON, AND INCIDENCE BY MONTHS OF MENINGOCOCCIC MENINGITIS

1917	Strength of Command	Incidence per 1,000
October.....	12,000	0.00
November.....	15,000	0.00
December.....	15,000	0.26
1918		
January.....	15,000	0.26
February.....	15,000	0.06
March.....	15,000	0.06

THE "CARRIER" PROBLEM

The first patient with meningococcus meningitis, a civilian laborer, was admitted Sept. 23, 1917. During the week beginning Oct. 16, 1917, sixteen patients were admitted. Since the isolation of carriers was believed to be the best means of combating the spread of the infection, all contacts were cultured by the laboratory staff. We are indebted to Major O. F. Broman, M.C., Chief of Laboratory Service, for the following data covering the enormous amount of work completed by the laboratory staff in the investigation of the problem.

The first 2,557 cultures from contacts revealed 2.5 per cent. carriers. As the work progressed it became apparent that the demonstration of infection, transmitted from patients with the disease to contacts, or from carriers to contacts, was difficult if not impossible, because of the widespread distribution of the infection. It was then determined to culture the entire command at Camp Funston and the Medical Officers' Training Camp at Fort Riley. This was continued as new recruits arrived, with the result that every soldier had repeated cultures. Table 10 shows the number of cultures taken by weeks, the percentage of carriers and the number of patients admitted.

During the period of nine months over 195,900 cultures were taken. It will be observed from the table that approximately 2 per cent. showed positive cultures for meningococci for the entire series. During three different weeks the percentage of positive cultures was over 5 per cent.: from October 29 to November 5 with eighteen meningitis admissions; from November 19 to November 26 with sixteen admissions, and from January 21 to January 28 with six admissions.

For short intervals, in small groups, the number of carriers would approximate 20 per cent., but the highest average for any week was 6 per cent.

TABLE 10.—MENINGITIS CARRIERS.

Date	Cultures	Carriers	Per Cent. Carriers	Cases
September 23 to September 30.....	0	0	0	2
October 15 to October 29.....	2,537	64	2.5	16
October 29 to November 5.....	1,746	105	6.0	18
November 5 to November 12.....	1,437	57	3.9	17
November 12 to November 19.....	3,044	78	2.5	22
November 19 to November 26.....	3,030	175	5.7	16
November 26 to December 3.....	7,343	120	1.6	10
December 3 to December 10.....	7,478	313	4.2	8
December 10 to December 17.....	10,674	275	2.6	7
December 17 to December 24.....	12,011	249	2.0	8
December 24 to December 31.....	7,930	321	4.0	9
December 31 to January 7.....	9,185	302	3.2	1
January 7 to January 14.....	12,814	285	2.2	6
January 14 to January 21.....	12,271	362	2.1	6
January 21 to January 28.....	10,653	506	5.6	6
January 28 to February 4.....	8,813	359	4.0	6
February 4 to February 11.....	11,434	226	1.8	4
February 11 to February 18.....	4,931	39	0.8	2
February 18 to February 25.....	1,207	67	0.5	4
February 25 to March 4.....	5,502	134	2.4	3
March 4 to March 11.....	3,263	43	1.3	4
March 11 to March 18.....	4,074	36	0.8	3
March 18 to March 25.....	4,748	22	0.5	3
March 25 to April 1.....	5,126	14	0.2	2
April 1 to April 8.....	3,718	12	0.3	2
April 8 to April 15.....	6,197	19	0.3	3
April 15 to April 22.....	1,572	3	0.2	1
April 22 to April 29.....	2,066	2	0.1	1
April 29 to May 6.....	5,352	9	0.2	3
May 6 to May 13.....	4,141	4	0.09	2
May 13 to May 20.....	263	0	0.0	2
May 20 to May 27.....	1,768	2	0.1	1
May 27 to June 3.....	3,377	2	0.05	2
June 3 to June 10.....	3,828	2	0.05	0
June 10 to June 17.....	47	0	...	1*
June 17 to June 24.....	691	0	...	0
June 24 to July 1.....	5,091	0	...	0
July 1 to July 8.....	4,394	0	...	0
July 8 to July 15.....	5,199	0	...	0
Total.....	193,904	4,197	2.1	201†

* Abortive type, no organisms found.

† Includes 10 mixed infections with meningococcus listed in Table 3.

It will be observed in Table 11 that the percentage of carriers showed little variation during the months of October, November, December and January, and yet there were about three and one-half times the number of admissions for meningitis in November as in January. Such facts, while admitting various interpretations, leave open to serious doubt certain established theories that the "carrier" markedly influences, except in a sporadic manner to susceptible individuals, the spread of epidemic meningitis. (See Graphic Chart 2.)

It is believed that individuals during the course of an epidemic in a military organization, who are known by repeated cultures to be chronic carriers should be isolated in a detention camp, there to be kept in the open air so far as possible and to receive treatment in the way of mild nasopharyngeal sprays and gargles. A 2 per cent. silver nucleinate nasal spray administered three times daily is slightly

astrigent and irritating to the mucous membrane and causes a more or less copious flow of secretion which mechanically assists in the removal of infection. A nasal spray of warm physiologic sodium chlorid solution is likewise efficient. A gargle of Liquor Sodii Boratis Compositus (N. F.) to which has been added 1 drop of phenol to the ounce is likewise useful. A week of such treatment is probably as efficient as a longer period.

MENINGITIS

UPPER SOLID LINE HOSPITAL
ADMISSIONS BY WEEKS

LOWER BROKEN LINE
PERCENT OF CARRIERS
IN TROOPS BY WEEKS

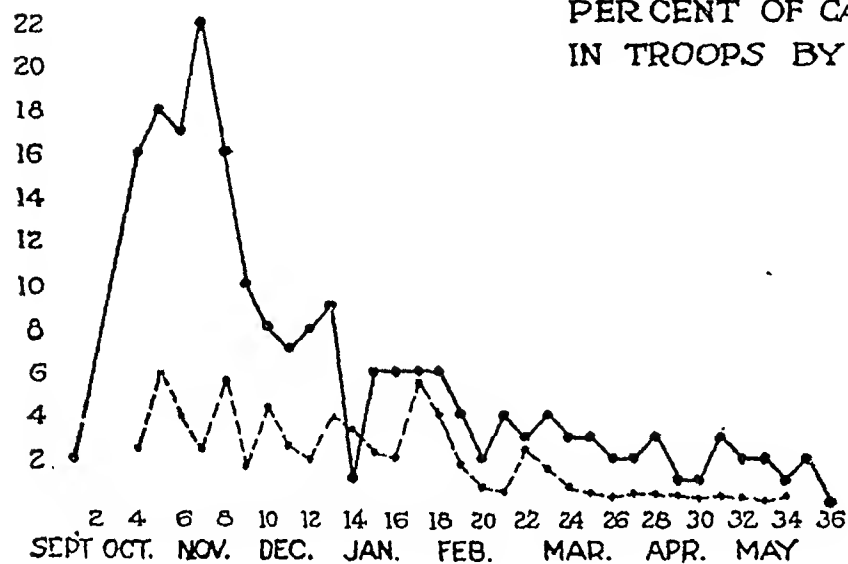


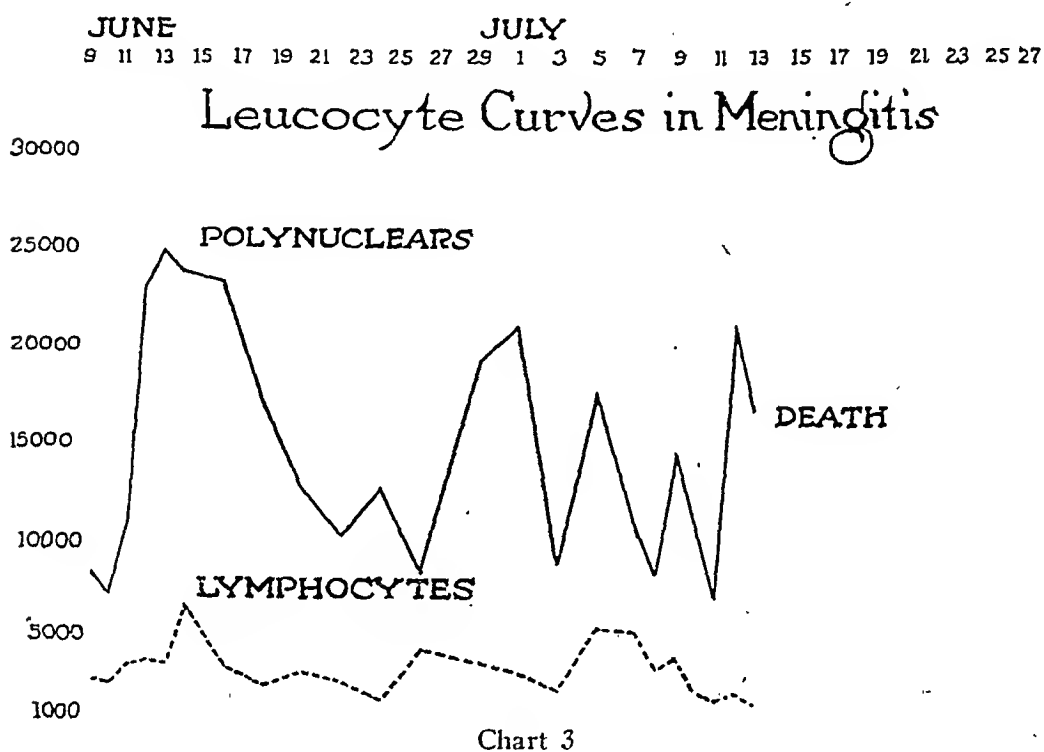
Chart 2

Since a very large percentage of all individuals are immune it is extremely doubtful if any considerable number of carriers can be detected early enough during the beginning of an epidemic greatly to influence its spread. Those who are specifically susceptible will undoubtedly acquire the infection when exposed directly to virulent organisms by sneezing or coughing carriers.

TABLE 11.—PERCENTAGE OF CARRIERS AND ADMISSIONS BY MONTHS COMPARED

	Average Carriers, per Cent.	Number of Meningitis Admissions
October 15 to November 5.....	4.25	34
November 5 to December 3.....	3.42	65
December 3 to December 31.....	3.20	32
December 31 to January 28.....	3.27	19

In the consideration of the carrier problem it is believed that a carrier is not necessarily a menace to other individuals unless it can be proved that he harbors virulent organisms. Two methods of transmission of the disease may occur. In the one avirulent organisms are transmitted to an individual who is specifically susceptible. Such an individual may or may not develop manifestations of the disease, depending on a variety of factors, such as fatigue accompanied by poor food and lack of sleep, or the presence or absence of other secondary or coincident infections present in an ordinary coryza, which might temporarily exalt virulence. In the other, virulent organisms are



transmitted to an individual with specific susceptibility, but whose immunity temporarily is such that he may for weeks manifest no disease and eventually rid himself of the infection harbored in his nasopharynx. Or he may become hypersusceptible through a variety of inimical influences and the disease become evident.

It is believed that culturing of contacts known to have been more or less closely associated with individuals who manifest the disease should be carried out. This refers in a military organization to close bed associates in the barracks or close table associates in the mess halls. Contacts who show positive cultures should be isolated for at least one week and receive the simple treatment described. Such patients should be kept in the fresh air and sunlight as much as possible.

IMMUNITY IN MENINGITIS

In the series embraced by this study, ten patients out of 191 patients with meningococcic meningitis, or 5 per cent., gave a history of an earlier carrier state. Of these ten patients, eight recovered and two died. It was not possible, because of the stress of work, to take nasopharyngeal cultures of all meningitis patients on admission, but during a series of cultures at different intervals it was found that approximately 10 per cent. of the cultures were positive.

A definite history of earlier meningitis was given by two patients, one of whom recovered while the other resulted fatally. Two patients were readmitted with meningitis several weeks after their recovery

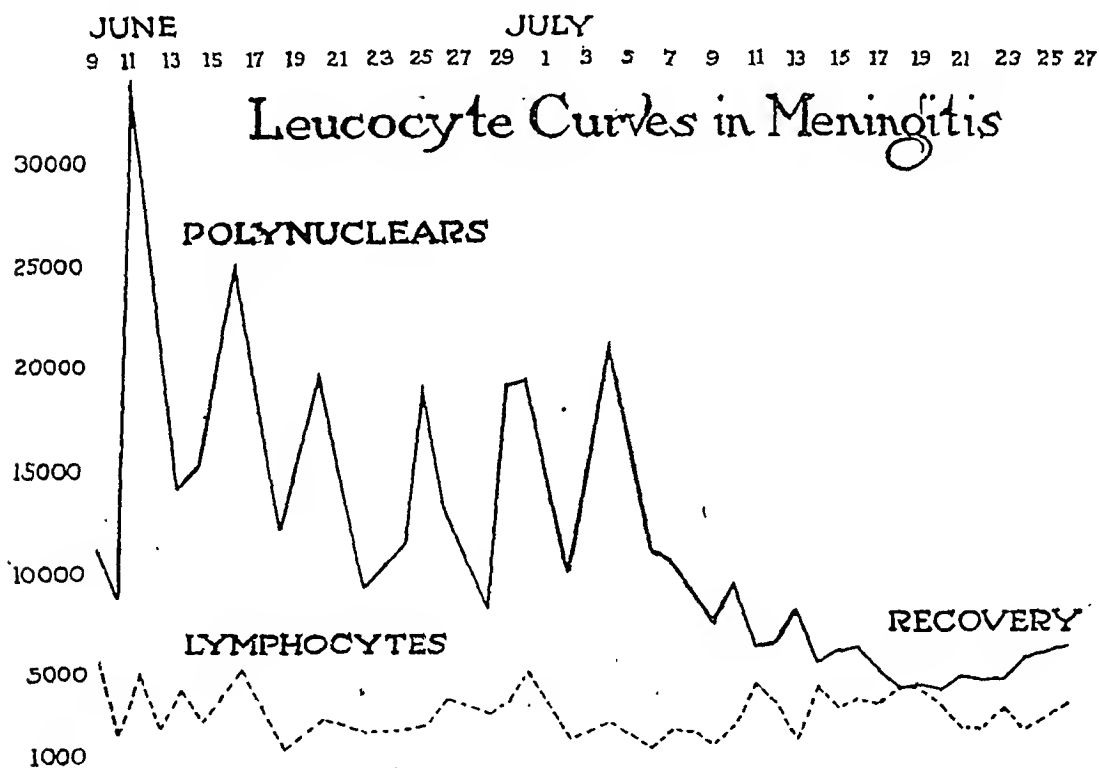


Chart 4

from the first attack. The first patient was in the hospital for thirty-two days with a typical moderately severe attack. Sixty-five days after his discharge from the hospital he was readmitted unconscious in a second attack, from which he recovered in thirty-three days. In a little over four months he had suffered two attacks of meningitis. The second patient was in the hospital forty-two days with a moderately severe meningitis. Eighty-four days after his discharge he was readmitted in a typical attack. He was sensitized to serum from the earlier intraspinal injections for, despite attempts at desensitization, the injection on the first three days of small quantities of serum intravenously was followed by severe anaphylactic reactions. This patient

presented an added difficulty in the way of treatment, since ventricular or spinal blockage had occurred from the earlier attack, and it was impossible to secure enough spinal drainage to give injections of serum into the canal. Severe headache, high fever and mild delirium occurred at irregular intervals. Injections of sensitized vaccine were begun in doses of from 500 to 2,000 millions every alternate or third day, with marked improvement in his condition. In all about twelve injections were given. He was discharged recovered four months after the onset of his second attack.

SYMPTOMS

The disease manifested itself, in most instances, by the sudden onset of headache, stiff neck, nausea or vomiting and chills, followed in a few hours by delirium and coma. So rapid was the onset in many instances that patients who complained of slight headache and nausea at bedtime were found unconscious in their beds the following morning. Table 12 shows the subjective initial symptoms in 136 recovered and fifty-five fatal instances of the disease.

TABLE 12.—INITIAL SYMPTOMS

Subjective Initial Symptoms in 136 Recovered Instances*		Subjective Initial Symptoms in 55 Fatal Instances*	
Symptoms	Per Cent.	Symptoms	Per Cent.
1. Headache.....	85	1. Stiff neck.....	46
2. Stiff neck.....	72	2. Nausea and vomiting.....	32
3. Nausea and vomiting.....	70	3. Headache.....	30
4. Chills.....	41	4. Fever.....	22
5. Fever.....	32	5. Chills.....	16
6. Sore throat.....	12	6. Backache.....	1.3
7. Backache.....	8	7. Coryza.....	1.3

* It is highly probable that the actual percentages of many of these symptoms should be higher but were not recorded on examination. For practical purposes they represent the relative sequence of subjective symptoms. In addition, photophobia should be mentioned as an especially suggestive symptom.

Fever was associated with chills or chilly sensations in one-third of the cases, while an inflamed pharynx, backache or coryza was mentioned less frequently.

Objectively, on admission, Kernig's sign was mentioned on the clinical history in 67 per cent. of 136 recovered instances. It is highly probable that in many cases this sign, as well as other symptoms, were omitted from the clinical record due to the stress of work, although found to be present at the time of examination. Kernig's sign has been in our experience almost universally present in meningitis, if not during the first twelve hours it is usually easily demonstrated at some time during the first twenty-four or thirty hours after the onset of

headache and neck rigidity. Stupor and coma were present in 51 per cent. of the recovered patients on admission, delirium in 29 per cent., exaggerated reflexes were mentioned in 23 per cent., dilated pupils in 22 per cent., and herpes labialis in 8 per cent. Petechiae were evident in only 6 per cent. of 136 recovered patients, but were present in 14 per cent. of fifty-five fatal instances. A leukocytosis varying from 15,000 to 35,000 was an important early symptom.

TABLE 13.—OBJECTIVE INITIAL SYMPTOMS

Objective Initial Symptoms in 136 Recovered Instances of Meningitis		Objective Initial Symptoms in 55 Fatal Instances of Meningitis	
Symptoms	Per Cent.	Symptoms	Per Cent.
1. Kernig's sign.....	67	1. Stupor and coma.....	42.6
2. Stupor and coma.....	51	2. Delirium.....	40.0
3. Delirium.....	29	3. Kernig's sign.....	37.0
4. Exaggerated reflexes.....	23	4. Dilated pupils.....	21.0
5. Dilated pupils.....	22	5. Petechiae.....	14.0
6. Babinski's sign.....	15	6. Retention urine.....	13.3
7. Herpes labialis.....	8	7. Exaggerated reflexes.....	9.3
8. Retention urine.....	6.7	8. Babinski's sign.....	8.0
9. Strabismus.....	6	9. Local convulsive movements....	5.3
10. Petechiae.....	6	10. Recent mastoidectomy.....	5.3

ABORTIVE TYPES OF MENINGITIS

Abortive types of epidemic meningitis are not uncommon and present great difficulties in proper recognition and care. We have seen many patients who presented during the course of an epidemic symptoms of the disease, headache, fever, vomiting, rigid neck, photophobia and Kernig's sign, but in whose spinal fluid meningococci could not be found. The fluid in such cases was under increased pressure and contained a moderate number of polymorphonuclear leukocytes. In searching for organisms in such cases the fluid should be centrifuged at high speed and 1 c.c. from the bottom of the tube allowed to dry on a glass slide before staining. The blood culture has been sterile in these patients.

In such abortive types with marked clinical evidences of the disease, especially in the presence of an epidemic, serum should be administered after free drainage at the time of diagnostic puncture. The clinical evidences in such instances markedly decreased after twenty-four hours, and recovery was complete in from seven to ten days. The recognition of such abortive types has been difficult in some patients because of the possibility of meningismus associated with a beginning pneumonia, the presence of acute cerebrospinal syphilis, of early tuberculous meningitis or of catalepsy or hysterical states associated with fever.

COMPLICATIONS

The serum rash and arthritis which occurred in about 30 per cent. of the recovered cases were of transitory duration as a rule. As mentioned in Table 14, in only one instance did culture from aspirated joints show meningococci. Temporary deafness occurred in about 7 per cent. of the recovered patients. Permanent nerve deafness, bilateral, occurred in 3.6 per cent. It came on early and suddenly and was the most distressing and disabling complication. Mixed infection was the most serious complication as to prognosis.

TABLE 14.—COMPLICATIONS IN 139 RECOVERED INSTANCES OF MENINGITIS

	Per Cent.		Per Cent.
Serum rash.....	30.0	Adenitis nonsuppurative.....	2.2
Arthritis.....	24.0*	Erysipelas.....	1.4
Parotitis.....	8.6	Multiple abscesses.....	1.4
Temporary deafness.....	7.2	Permanent deafness (partial).....	1.4
Orchitis.....	4.3	Paralysis of arm (temporary).....	1.4
Otitis media.....	4.3	Paralysis of palate (partial).....	0.7
Tonsillitis acute follicular.....	4.3	Paralysis of trunk (partial).....	0.7
Permanent deafness (total).....	3.6	Paralysis of deltoid.....	0.7
Cornical ulceration.....	3.6	Paralysis of tongue.....	0.7
Rubecula.....	2.9	Paralysis of peroneus (permanent)	0.7
Cystitis.....	2.9	Neuritis of extremities.....	0.7
Lobar pneumonia.....	2.2	Phlebitis.....	0.7
Adenitis suppurative.....	2.2†	Panophthalmitis, enucleation of eye.....	0.7

* Arthritis developed in most instances about the time of serum rash and was probably due to the same cause. In only one instance did culture from aspirated joints show meningococci.

† Due to streptococcus infection.

‡ Cultures from vitreous humor revealed growth of meningococci.

TABLE 15.—COMPLICATIONS IN 76 FATAL INSTANCES OF MENINGITIS

	Per Cent.
Mixed infection (pneumococcus or streptococcus with meningococcus).....	15.8
Serum rash.....	4.0
Otitis media.....	4.0
Lobar pneumonia.....	4.0
Lobar pneumonia with pneumococcal meningitis.....	2.6
Mastoiditis suppurative with Type I pneumococcal meningitis.....	1.3
Mastoiditis with streptococcal meningitis.....	2.6
Skull fracture with streptococcal meningitis.....	1.3
Fracture of ileum and peritonitis.....	1.3
Streptococcal peritonitis (cause not found).....	1.3
Inanition.....	1.3
Nephritis acute.....	1.3
Optic neuritis.....	1.3
Facial paralysis.....	1.3

PATHOLOGY

Complete records of twenty-six necropsies were available in this series. In the epidemic form the following conditions were usually found. The brain was irregularly covered with a fibrinopurulent exudate. This exudate was most marked along the course of the larger blood vessels of the cortex, about the points of exit of the cranial nerves and at the base over the pons and medulla. Usually,

marked edema of the brain was present, with obliteration of the sulci of the cortex. The pia-arachnoid vessels of the cortex were markedly injected. Punctiform hemorrhages were frequently noted in the ventricular spaces, which were dilated and contained cloudy fluid. The cavities of the third and fourth ventricles frequently contained a fibrinopurulent exudate which covered the choroid plexus. Punctiform hemorrhages also were found in the corpus striatum.

In some instances the entire spinal cord was enveloped with exudate. This was usually more marked over the posterior surface and involved the point of exit of spinal nerve roots. Walled-off pockets, with obliteration of the subarachnoid space, were found in some instances, which accounted for difficulties in securing adequate spinal drainage. The exudate was made up of polynuclear leukocytes and fibrinous debris.

Hypostatic pneumonia was frequently found to be present in those patients who had been ill a number of weeks. This was usually associated with edema. Acute or subacute cloudy swelling of the kidneys, liver, spleen and myocardium was usually present. Cultures from the brain and cord in nearly every instance revealed meningococci, while cultures from spleen, heart blood, liver and kidneys were negative.

In septic meningitis due to streptococci or pneumococci, middle ear disease, frequently bilateral, acute mastoiditis, ethmoiditis or empyema of the sinuses was frequently found. In two instances which followed a putrid bronchitis the primary focus of infection was found to have arisen from abscess of the lung. Direct extension of the infection to the meninges from infected mastoid cells prior or subsequent to operation was not common. The organisms present in such cases were usually hemolytic streptococci or pneumococci. In a number of instances of meningitis subsequent to mastoiditis, meningococci were found in the spinal fluid, while the secretion from the mastoid contained streptococci or pneumococci. These patients were probably meningococcic carriers at the time of the onset of the mastoiditis, or were exposed to a carrier after the onset of the mastoid infection.

TREATMENT

Lumbar puncture was performed for diagnostic purposes as early as possible on all meningitis suspects, either in the Receiving Ward where the patients were isolated in cubicles, or in a separate cubicled suspect ward adjacent to the meningitis section. If the fluid was under considerable pressure, drainage was allowed to proceed until the pressure approximated the normal, one drop every three or four seconds. If the fluid was cloudy, an injection of 30 c.c. of serum was given without waiting for the laboratory report. In some instances the

fluid was under increased pressure but was clear, in which case, if the clinical symptoms were sufficiently suggestive, an injection of serum was given at the time of diagnostic puncture.

The fluid in streptococcus or mixed infection meningitis, as a rule, had a straw-yellow tinge, while the fluid of meningococcus meningitis had a grayish-white opaque appearance. After several intraspinal injections of serum had been given, the spinal fluid became slightly yellowish in the treated patients. In numerous instances despite great care on the part of the officers in the laboratory especially detailed for the examination of spinal fluids, no organisms would be found in the centrifugalized fluid obtained from the first and, in some instances, the second punctures. Again, in a series of punctures organisms would be found on one occasion only. As a rule, however, there was little difficulty in finding the organisms in the fluid obtained by the daily puncture. A daily specimen of fluid was sent to the laboratory from each patient. In 90 per cent. of 215 instances the spinal fluid was distinctly cloudy on first puncture.

TABLE 16.—THE SPINAL FLUID IN MENINGITIS, FIRST PUNCTURE

Recovered 139	Per Cent.	Fatal 76	Per Cent.
1. Cloudy.....	91.3	1. Cloudy.....	88.1
2. Clear but with leukocytes microscopically and positive globulin.....	6.4	2. Clear but with leukocytes microscopically and positive globulin.....	9.2
3. Clear with no leukocytes or globulin.....	1.4	3. Clear but organisms found.....	2.6
4. Clear but organisms found.....	0.7		

The usual amount of serum given intraspinally was from 30 to 35 c.c. twice daily during the first five or six days until the reports received from the laboratory showed two or more negative examinations. The amount of drainage of spinal fluid depended on its pressure, whether headache became more marked during the procedure or whether, as happened in many instances, relief of headache and restlessness was secured by it. As a rule, the quantity of fluid drained exceeded by from 15 to 25 c.c. the quantity of serum to be given. The average amount of serum drained was approximately 50 c.c., but in a number of instances quantities varying from 70 to 85 c.c. were obtained without markedly decreasing the pressure, in which case larger quantities were secured. In Table 17 it will be noticed that the average number of intraspinal treatments in 136 recovered patients was eleven; the average total amount of serum received by each was 305 c.c., the average total drainage of spinal fluid was 571 c.c. The average stay in the meningitis section among these recovered patients was fifty-two days.

Among the fifty-five fatal instances of meningococcic meningitis the average number of intraspinal injections was ten; the average total amount of serum given was 310 c.c., while the average total amount of fluid drained was 558 c.c. The average number of days under treatment in these fatal instances was 10.5.

TABLE 17.—DATA OF TREATMENT

	Meningococcus Meningitis		Mixed Infections	
	Recovered	Fatal	Recovered	Fatal
Number of patients.....	136	55	1	12
Average number I. S. injections.....	11	10	12	6
Average total amount serum, c.c.	305	310	415	151*
Average total spinal drainage, c.c.....	571	558	475	251
Days in hospital.....	52	10.5	147	9

* Antistreptococcus, antimeningococcus or antipneumococcus serum.

INTRAVENOUS THERAPY

Much interest has followed the treatment recently advocated by Major Herrick¹ and by Netter² of combined intravenous and intraspinal therapy in meningitis. In a large percentage of the cases reported by Herrick from Camp Jackson, South Carolina, petechiae were common during the initial stage of the disease. This led to the belief that early in the course of the disease the blood stream was infected, followed later by localization in the meninges. This logical assumption is apparently true for certain types of meningococcus infection, but that it is true for all types is not so easily proved. In this series but 6 per cent. of the recovered patients showed petechiae. Among the fatal instances, 14 per cent. showed petechiae. Included among these were the rapidly fulminating types with death in a few hours. In some of these the cerebrospinal evidences of the disease were found to be slight on necropsy, although the meningococcus was obtained by culture. The evidence pointed to early blood stream invasion with death from sepsis. The following abstracts of clinical histories illustrate this point:

CASE 1.—April 11, the patient was admitted to the hospital with transfer diagnosis of influenza. He complained of headache. In a few hours a syncopal attack occurred, with involuntary micturition, followed by transitory delirium and muscular contractures in the extremities. A stuporous condition soon supervened. Lumbar puncture showed only a few leukocytes; no organisms. Kernig's sign was positive. General adenitis was present, but his neck was only slightly rigid. The second lumbar puncture did not reveal meningococci, but 40 c.c. of antimeningitis serum were given intraspinally and 60 c.c. intravenously. Death occurred in about twenty-four hours from time of onset. Large hemorrhagic spots the size of the hand appeared over both ankles and on the face, with smaller petechiae scattered over the trunk about six hours before death. These spots coalesced until at time of death the body was covered with confluent areas, with but small areas of white skin remaining. At

1. J. A. M. A. **71**:612, 1918.
2. Rev. de méd. **35**:133, 1917.

necropsy there was no gross evidence of meningitis, but cultures of small suspicious foci showed meningococci. The nasopharyngeal culture and the blood culture showed meningococci.

CASE 2.—The patient, a civilian, previously well, was suddenly taken with chill, nausea and vomiting. His general condition became rapidly worse during the following eleven hours; the extremities became cyanotic and large hemorrhagic spots appeared over the body. Three hours later he was admitted to the hospital; temperature 104, pulse 170, barely perceptible at the wrist; respiration was embarrassed and he was stuporous. The spinal fluid was clear, with but few cells. A few extracellular meningococci were found. Two intraspinal injections of serum were given (80 c.c.) and three intravenous injections (140 c.c.) during the following eighteen hours. Death occurred in thirty-two hours after onset. The blood culture showed meningococci.

TABLE 18.—COMBINED INTRASPINAL AND INTRAVENOUS THERAPY IN MENINGOCOCCUS MENINGITIS

Recovered				Died				
Number Injections, Intravenous	Total Amount Serum, C.c.	Number Injections, Intraspinal	Total Amount Serum, C.c.	Number Injections, Intravenous	Total Amount Serum, C.c.	Number Injections, Intraspinal	Total Amount Serum, C.c.	Days Under Treatment Before Death
1	20	10	350	18	730	20	460	29
1	100	7	140	3	140	2	80	1
9	300	15	380	11	420	9	340	17
4	140	9	255	1	80	13	240	12
6	140	13	320	1	20	3	60	2½
5	100	8	260	10	360	35	1,080	30
9	190	11	260	1	60	1	40	1
11	220	17	380	2	40	10	255	6
10	350	13	310	4	200	40	1,015	41
11	320	13	290					
8	210	17	395					
5	100	25	555					
3	60	0	0*					
2	40	10	275					
3	70	9	225					
3	60	17	490					
4	75	9	285					
4	75	13	365					
4	80	7	240					
3	60	8	240					
2	40	9	250					
2	35	7	230					
4	170	31	795					

Recovered:	
Average number intravenous injections.....	5
Average total amount serum received.....	130 c.c.
Average number intraspinal injections.....	13
Average amount serum received.....	329 c.c.
Total patients, 23	
Deaths:	
Average number intravenous injections.....	5
Average total amount serum received.....	228 c.c.
Average number intraspinal injections.....	15
Average total amount serum received.....	397 c.c.
Total patients, 9	

Mortality in 32 instances having combined treatment, 28.1 per cent.

Twenty-six patients received more than 50 c.c. serum intravenously, while seventeen patients received 100 c.c. or more.

* Readmitted patient with ventricular or canal blockage from earlier attack, in whom it was impossible to give serum intraspinally.

Table 18 describes the use of combined therapy in thirty-two patients. The mortality was 28.1 per cent. Three of the patients died within sixty hours after admission. In one of the fatal cases the patient received 730 c.c. of serum intravenously in eighteen injections, and 460 c.c. of serum intraspinally in twenty injections; in two other fatal cases the patients received 200 and 360 c.c., respectively, by vein and 1,080 and 1,015 c.c., respectively, into the spinal canal. The mortality in this series of patients was almost identical with the mortality among 159 patients with meningococcic meningitis treated intraspinally (deaths forty-six; mortality 28.9 per cent.). The criticism

may be offered that enough serum was not given by vein to some of these patients. To this it may be replied that as much was given as appeared advisable at the time, because of the occurrence of symptoms of anaphylaxis.

We feel that patients manifesting petechiae, as evidence of blood stream invasion, should receive intravenous injections of serum in doses of from 60 to 100 c.c. daily during the first three or four days of the disease, as well as intraspinal injections varying from 30 to 40 c.c. of serum twice daily. If success is to be secured, early energetic treatment is essential, and is of greatest value during the first three or four days. Although we believe that the blood stream infection is transitory, with relatively early localization in the meninges, the method of combined intravenous and intraspinal therapy should receive thorough trial.

REMARKS ON TREATMENT

During the course of treatment in a number of instances the spinal fluid became decreased in quantity, which made it exceedingly difficult to administer intraspinally a sufficient amount of serum without danger of increased pressure. In such cases it was assumed that ventricular or canal blockage had occurred. If the attempt was made at such a time to give intravenously, after desensitizing doses of 0.5 c.c. subcutaneously, followed in an hour by 1.0 c.c., chills and collapse, symptoms attributed to anaphylaxis, occurred. Cyanosis with rapid pulse and dyspnea followed in some instances. These symptoms, although alarming, were usually alleviated in from ten to twenty minutes by an injection subcutaneously of 10 or 15 minims of 1 to 1,000 solution epinephrin chlorid. If the dosage by vein was repeated, a hypodermic injection of atropin, 1/100 grain, or of epinephrin prevented the onset of such symptoms.

If the treatment was begun early in the disease by vein as well as by spinal canal the symptoms enumerated rarely occurred; it was only after several days of intraspinal treatment that symptoms occurred if the attempt was made to inject by vein. The method of injection of serum by vein was the same in both instances. The serum was warmed by placing the bottle, connected with a three-way stop-cock and syringe, in a pan of water. The injection of serum was given slowly at a rate of 1 c.c. per minute for the first 15 c.c. If evidences of serum reaction occurred the injection was stopped and the attempt made twelve hours later after a preliminary injection of atropin, 1/100 grain, or epinephrin chlorid solution.

The point is made that in a patient still manifesting evidences of the disease, such as positive organisms or fever, in whom mechanically it becomes difficult to continue treatment by spine, the attempt should

be made to give serum by vein. In a fairly large percentage of such cases serum reactions will occur, but it is believed that the danger of such reactions, especially if atropin or epinephrin is used, and if desensitization has been properly carried out, is infinitely less than the danger of stopping all serum treatment. If it is believed after a number of treatments that little progress is being made, the agglutinative titer of the serum should be determined against pure cultures of the organism. A potent polyvalent serum should agglutinate in dilution 1 to 200, or higher, the usual strains of meningococci, using normal horse serum in dilution of 1 to 100 as a control. If the serum used does not give such agglutination, another make of serum should be tried. It is highly desirable in the presence of an epidemic to determine by agglutination tests the prevailing type of meningococcus encountered. This may be done by the use of monovalent rabbit serum furnished by the Army Medical School against the strains produced by the Rockefeller Institute, namely, Normal No. 1; Intermediate A. No. 10; Intermediate B. No. 30 and Parameningococcus No. 60.

Epinephrin chlorid injections subcutaneously of 15 minims of the 1 to 1,000 solution usually promptly relieved the urticaria which was so commonly seen between the seventh and tenth days of treatment. The administration of morphin was necessary in many instances to relieve restlessness and was believed to be an important adjunct in treatment at any time during the acute stage. For the treatment of herpes labialis alkalization by soda bicarbonate or the so-called "Imperial Drink"³ may be recommended. Since herpes labialis has been recognized as associated with acidosis, our patients have been given alkalies routinely with the result that these lesions have been much less evident in the wards. If difficulty is experienced in giving alkalies by mouth, the following may be given by the drop method per rectum: dextrose 30.0; sodium bicarbonate 15.0; tap water 1,000.0.

The question when to stop the treatments by spine has been a difficult one in many instances. The spinal fluid may have contained no organisms after two or three treatments and then a week or ten days later organisms would be found. If the patient had been doing well with but slight elevation of temperature and a decreasing actual and polymorphonuclear differential count, and had had eight or ten treatments, free spinal drainage for a few days was in most instances all that was required. It was not believed, after supposed saturation with serum, that much benefit was secured by further serum injections. We have seen distinct harm produced by overzealous administration

3. Imperial Drink consists of cream of tartar one teaspoonful, sodium citrate and sugar, of each one-half teaspoonful, water flavored with orange or lemon juice, sufficient to make 8 ounces.

of serum after quantities of from 300 to 400 c.c. had been given, solely because the fluid still contained organisms. One patient who had been extremely ill received, after a lapse of a week, an additional treatment by spine because organisms were found in small numbers after a period of negative reports. He became unconscious and remained so for about one week, from which he gradually recovered. We wish to lay stress, from our experience, on the fact that early intensive treatment is necessary to secure results, but we strongly feel that harm may be done by overtreatment after the first ten days or two weeks.

The fever, as a rule, gradually declined after a few treatments. If a remission occurred, associated with positive organisms, it was found advisable to give an additional treatment. The aim has been to be guided by these remissions as a useful index to the frequency of treatment after the first week.

PROGNOSIS

With decrease of fever occurring gradually during the first week, together with return of consciousness and a steady decrease in the actual and polymorphonuclear differential count, made every alternate day, the outlook as to life was good despite the fact that headache and neck rigidity persisted. From the work done by Capt. Edmond Holberg, M.C., in the meningitis wards we are reproducing two charts (3 and 4), which typify the prognostic value to be attached to the actual and differential leukocyte counts in this disease. The prodromal symptoms are important since their recognition leads to early diagnosis and treatment, on which the prognosis depends. These prodromal symptoms of malaise, depression, slight fever and muscular aching are associated with the development of other acute infections. In the presence of an epidemic such symptoms, with headache or nausea, assume great importance, especially if small petechiae are found on the trunk, face, mucous membranes of the mouth or in the conjunctivae. If the disease can be recognized early, and be efficiently treated, the mortality should not be greater than 20 per cent., which would be in marked contrast to statistics covering the period before the adoption of a potent antiserum. The future promises still greater reduction as experience and judgment in its use accumulates, especially in the use of convalescent human serum for the treatment of the acute disease, a plan for which has been worked out in this hospital.

SUMMARY

1. Eighty-nine per cent. of patients with meningitis in the series here reported were from rural districts.
2. The incidence of meningococcus meningitis to hospital admissions in eight and one-half months was 0.77 per cent. The highest

incidence of the disease in any month was 2.57 per thousand white troops and 0.26 per thousand colored troops.

3. The largest number of patients were from the states of Kansas and Missouri, which have for a number of years been recognized as endemic meningitis areas.

4. The mortality in 191 instances of epidemic meningitis was 28.8 per cent.

5. The mortality in thirteen instances of meningitis due to mixed infections, such as streptococcus or pneumococcus with meningococcus, was 92.3 per cent.

6. The mortality in eleven instances of meningitis due to other organisms than the meningococcus was 81.8 per cent.

7. Among 175 white patients with meningococcus meningitis the mortality was 29.7 per cent.; among sixteen negroes the mortality was 18.7 per cent.

8. During the course of the epidemic 196,000 cultures were taken for carriers. The highest percentage of carriers found was 6 per cent.; the average for the entire series 2.1 per cent.

9. Five per cent. of patients with meningitis had been under treatment for the carrier state at an earlier date.

10. The spinal fluid was cloudy in 90 per cent. of first punctures. The fluid was clear, but organisms found, in less than 1 per cent. of the recovered patients and in 2.6 per cent. of the fatal instances.

11. The average number of intraspinal treatments in 136 recovered patients was eleven; the average total amount of serum each received was 305 c.c.; the average total spinal fluid drainage was 571 c.c. The average period of illness was fifty-two days.

12. Among fifty-five fatal instances the average number of days under treatment before death was 10.5.

13. Six per cent. of the recovered patients and 14 per cent. of the fatal instances exhibited petechiae.

14. Positive blood cultures were obtained in a larger percentage of patients with petechiae, while negative blood cultures were as a rule obtained in those patients not manifesting petechiae.

15. The mortality among thirty-two patients who received combined intravenous and intraspinal therapy was 28.1 per cent.

CONCLUSIONS

1. The early diagnosis of abortive types of meningitis, especially during an epidemic, is important.

2. Although recognizing the importance of carriers and their relationship to instances of the acute disease, it is doubtful if carriers can be detected early enough during the course of an epidemic to limit its spread.

3. Intimate contacts, such as tent mates, close bed associates in the barracks and close mess table associates should be cultured upon the development of a case of the disease. If a carrier is found he should be isolated, receive the simple treatment before outlined, and be kept in isolation until four or five negative nasopharyngeal cultures have been returned. These may be taken at two-day intervals.

4. Early energetic treatment is of greatest importance. This embodies, especially in those manifesting petechiae, intravenous and intraspinal therapy. The following plan is recommended: First day, one intravenous injection of from 60 to 80 c.c. serum and two intraspinal injections of from 30 to 40 c.c. each after spinal drainage of from 45 to 55 c.c. of fluid, depending on its pressure; second day, same, except that from 80 to 100 c.c. of serum should be given intravenously, and two spinal injections; third and fourth days, if necessary; repeat; fifth to eighth day, one spinal injection; ninth and tenth days, one spinal drainage daily.

5. It has always proved wise to desensitize before giving the first intravenous injection, by a subcutaneous injection of 1 c.c. of serum. The intravenous injections should be given slowly, at the rate of 1 c.c. of warmed serum per minute for the first 10 or 15 c.c. If anaphylactic symptoms occur the injection should be stopped and the attempt repeated later. Epinephrin chlorid, 1 c.c. of the 1 to 1,000 solution, by hypodermic injection, relieves the symptoms of anaphylaxis. Atropin, grain 1/100, by hypodermic injection is also useful. The serum if mixed, not shaken, with an equal volume of salt solution is less apt to clog the needle.

6. If patients have been given a number of intraspinal treatments and subsequently an intravenous injection is contemplated, extreme care in its administration is necessary to avoid serious symptoms of anaphylaxis.

7. Overtreatment after the first ten or fourteen days may do positive harm.

8. The actual and differential polymorphonuclear leukocyte count is of value in prognosis.

NOTE.—Grateful acknowledgment is made to the following officers for service and suggestions during the course of the epidemic: Majors Andrew MacFarlane and Oscar F. Broman; Captains James W. Osborn, Henry J. Hayes, Robert L. Benson, Edward D. O'Neill, Clark W. Zugg, Edmond A. Holberg and Lieut. James R. Sanford.

PLASMAPHAERESIS IN THE TREATMENT OF CHRONIC NEPHRITIS AND UREMIA *

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In 1914 Abel, Rowntree and Turner¹ reported on the physiologic effects in dogs of bleeding, removing the plasma and returning the corpuscles after washing with Locke's solution. Such a process was appropriately designated "plasmapheresis," and it was shown by these authors and by Turner, Marshall and Lamson² that it could be carried to a very considerable extent with entire recovery of the experimental animal. The technic presented in these articles required the use of herudin for prevention of blood coagulation, and positive evidence was secured that the German preparation of herudin then on the market had toxic properties of high order.³ While the authors in question have offered a number of suggestions as to the possible practical use of plasmapheresis, the difficulty of the maneuver, coupled with the impossibility of using herudin, seems to have prevented its clinical employment. In the course of experiments designed to disclose the toxic elements in citrated blood transfusions it became expedient to obtain data on removal and return of corpuscles from the same individual. In consequence of this need the ordinary venesections in uremia patients, which would have been carried through without return of corpuscles, were made instances of plasmapheresis, and data were obtained on the possible beneficial effects of this measure. This material is deemed worthy of a brief report.

Technic.—The blood was drawn into sodium citrate, centrifugalized and prepared for return, as indicated in a previous article,⁴ except that in no case was sodium citrate added before reinjection, nor was Ringer's solution employed. Cases of chronic nephritis with hypertension are particularly favorable subjects for the necessary technic. It was our practice to withdraw 700 or 800 c.c.

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1. Abel, John J.; Rowntree, L. G., and Turner, B. B.: Jour. Pharmacol. and Exper. Therap. 5:625, 1914.

2. Turner, B. B.; Marshall, E. K., and Lamson, P. D.: Jour. Pharmacol. and Exper. Therap. 7:129, 1915.

3. Marshall, E. K.: Jour. Pharmacol. and Exper. Therap. 7:157, 1915.

4. Drinker, C. K., and Brittingham, H. H.: Archives Int. Med. 28:133 (February) 1919.

of blood, centrifugalize, wash twice with freshly made sterile 0.85 per cent. sodium chlorid solution and to return the corpuscles made up to the original volume with salt solution. On completing this return, and without inserting another needle, 700 or 800 c.c. of blood were again withdrawn. The corpuscles thus removed were washed twice and reinjected. The patient never experiences a hemorrhage of more than 800 c.c., and he is subjected to no operation except venepuncture, as it should never be necessary to cut down on a vein in such cases.

The removal of toxic products from 1,500 to 1,700 c.c. of blood cannot result in very large alteration in the patient's plasma. On several occasions we observed rather striking but brief subjective improvement in our patient, but are inclined to attribute it to the psychic effect of the formidable therapeutic maneuver to which the patient was subjected, rather than to any true benefit. The operation has been done eighteen times on eight patients, and the history of one case is presented. Other cases have been so similar as to merit no comment.

REPORT OF CASE

History.—Patient, D. J. McD., man, aged 49, Sept. 17, 1917.

Diagnosis.—Chronic nephritis, chronic uremia, hypertension.

Complaint.—General weakness, dyspnea and cough.

Family and Marital History.—Unimportant.

Habits.—Alcohol in excess.

Occupation.—Steamfitter.

Previous Medical History.—Measles and mumps in infancy. Good recovery and no complications. Weight 210 pounds, four years ago; has lost 53 pounds in the past four years.

Present Illness.—In 1912 the patient first noticed swelling about the ankles, particularly at night, but was not troubled by other symptoms until 1913, when he gradually began to have dyspnea, polyuria, especially nocturia, intense thirst and constant fatigue. Dizziness and violent headaches were soon added, and on one occasion he had an extremely severe nose bleed. By resting frequently the patient has kept at work, but has never felt really well. Vision has grown very bad. For the past twelve days he has been "all in," very dyspneic and drowsy, but unable to sleep. He is entirely unable to lie down on account of a "choking feeling."

Physical Examination.—A well-developed man, sitting upright in bed and showing occasional periods of dyspnea. He appears very ill. Face: Thin, very pale, pasty and expressionless. Eyes: There is external strabismus of the eye with ptosis of the left lid. No photophobia, lacrimation, diplopia, nystagmus, lid-lag or exophthalmos. Conjunctivae pale. The vision of the left eye is partially gone save for light, while that of the right is quite defective and blurred. Ophthalmoscopic examination: Left eye, pupil fixed, media clear, whole fundus pale and dotted with small hemorrhages. Disk covered with exudate and slightly elevated. Right eye, fundus pale. Above the disk there is a small patch of exudate and several hemorrhages. Vessels here, as in the left eye, are tortuous and pulsate slightly.

Thorax: Symmetrical; respirations 28, deep and regular. Heart: Apex impulse forcible in fifth space 12 cm. from midsternal line. No murmurs and no irregularities. Aortic second sound increased. Vessels: Marked sclerosis of radial and temporal arteries.

Blood pressure: Systolic, 225; diastolic, 185.

Lungs: Numerous râles are heard at both bases.

Edema: Moderate in both ankles. No fluid in abdomen or chest.

Further physical findings are unimportant. On admission the patient presented a typical instance of advanced chronic nephritis and hypertension with uremia.

September 17.

Laboratory Report.—Blood: Hemoglobin, 57 per cent. Red blood count, 2,040,000. White blood count, 12,200. Smear: Polymorphonuclears, 80 per cent.; lymphocytes, 15 per cent.; large mononuclears, 3 per cent.; eosinophils, 1 per cent.; mast cells, 1 per cent. Anisocytosis, macrocytosis and moderate achromia were noticed in red cells.

September 18.

Urine: Amber, pale, turbid, acid. Specific gravity, 1.013; large trace of albumin, no sugar. Sediment: occasional white blood corpuscles; large number hyaline, granular and epithelial casts. Phenolsulphonephthalein test, 20 per cent. in two hours (urine volume 175 c.c.).

September 19: The patient is sleepless and often incoherent. His dyspnea has not improved. Owing to the pronounced secondary anemia venesection does not seem advisable and plasmapheresis will be employed.

8:33 a. m., 700 c.c. of blood were withdrawn in the usual way into 25 c.c. of 8 per cent. sodium citrate, centrifugalized and red cells washed twice in freshly made sterile 0.85 per cent. sodium chloride solution, care being taken to discard all buffy material.

12 noon, 500 c.c. saline suspension of these red cells were injected. On finishing this infusion 750 c.c. of blood were withdrawn through the same needle into 25 c.c. of 8 per cent. sodium citrate solution. This blood was treated as in the first case.

2:10 p. m., 550 c.c. saline suspension of washed cells from second removal were injected.

Total amount of discarded plasma, 1,000 c.c.

Blood urea nitrogen, before plasmapheresis, 34.5 mg. in 100 c.c.; after plasmapheresis, 36.5 mg. in 100 c.c.

Plasma chlorids, before plasmapheresis, 5.62 gm. per liter; after plasmapheresis, 5.81 gm. per liter.

September 20: The patient feels much better, has slept well and is anxious to carry through the projected treatment. Plasmapheresis will be repeated today.

9:55 a. m., 700 c.c. of blood withdrawn into 25 c.c. 8 per cent. sodium citrate.

12:55 p. m., 500 c.c. saline suspension of these red cells injected. On finishing this infusion 650 c.c. of blood were withdrawn through the same needle and treated as in the first instance.

4 p. m., 650 c.c. saline suspension of washed cells from second removal were injected.

Total amount of discarded plasma, 900 c.c.

Blood urea nitrogen, before plasmapheresis, 34.7 mg. in 100 c.c.; after plasmapheresis, 35.6 mg. in 100 c.c.

Plasma chlorids, before plasmapheresis, 5.81 gm. per liter; after plasmapheresis, 6.03 gm. per liter.

September 21: Patient much improved and encouraged. He has had no unfavorable reaction of any sort from his two experiences with plasmapheresis.

September 24: Blood urea nitrogen, 30.9 mg. in 100 c.c.

Blood: Hemoglobin, 53 per cent.; red blood count, 2,848,000; white blood count, 13,300. Smear: polymorphonuclears, 86 per cent.; lymphocytes, 10 per cent.; large mononuclears, 4 per cent. Anisocytosis and achromia present as formerly.

September 25: The patient has been out of bed in a wheel chair. He now sleeps without orthopnea. Plasmapheresis will be repeated.

8:15 a. m., 800 c.c. of blood withdrawn into 25 c.c. 8 per cent. sodium citrate.

11:35 a. m., 575 c.c. saline suspension of these red cells injected. On finishing this infusion 700 c.c. of blood were withdrawn through the same needle and treated as in the first instance.

2:15 p. m., 575 c.c. saline suspension of washed cells from second removal injected.

Total amount of plasma discarded, 1,000 c.c.

Blood urea nitrogen, before plasmapheresis, 33.2 mg. in 100 c.c.; after plasmapheresis, 33.5 mg. in 100 c.c.

Plasma chlorids, before plasmapheresis, 5.26 gm. per liter; after plasmapheresis, 5.32 gm. per liter.

Urine: Amber, pale, slightly turbid, acid. Specific gravity, 1.006; large trace of albumin; no sugar. Sediment: occasional epithelial cell, rare red blood corpuscles; occasional granular cast.

September 28: The patient's anemia has not changed since entrance, and transfusion will be done as soon as a donor can be found. He has been up and about the ward for the last four days and has not felt any symptoms except fatigue. Systolic blood pressure remains constantly at 220 mm. Hg.

October 1: Patient received a transfusion of the washed red cells from 600 c.c. of blood from a properly matched donor. These cells were suspended in plasma from the same donor which had been cleared of formed elements by one hour of high speed centrifugalization. He had a very slight chill and temperature reaction following this transfusion.

Blood urea nitrogen, before transfusion, 40.7 mg. in 100 c.c.; after transfusion, 40.7 mg. in 100 c.c.

Plasma chlorids, before transfusion, 5.69 gm. per liter; after transfusion, 6.06 gm. per liter.

October 6: Blood urea nitrogen, 42.8 mg. in 100 c.c. Plasma chlorids, 5.53 gm. per liter.

October 13: The patient has remained constantly in bed since October 7 and has been failing steadily. Plasmapheresis again carried out.

9:30 a. m., 500 c.c. of blood withdrawn into 25 c.c. 8 per cent. sodium citrate.

12:30 p. m., 500 c.c. saline suspension of these red cells injected. On finishing this infusion 500 c.c. of blood were withdrawn through the same needle and treated as in the first instance.

3:30 p. m., 500 c.c. saline suspension of red cells from second removal injected; 600 c.c. of blood were withdrawn through the same needle and treated as usual.

6:15 p. m., 600 c.c. saline suspension of red cells from third removal were injected.

Total plasma discarded, 1,000 c.c.

Blood urea nitrogen, before plasmapheresis, 92.3 mg. in 100 c.c.; after first red cell return, 92.3 mg. in 10 c.c.; after second red cell return, 95.7 mg. in 100 c.c.

Blood chlorids, before plasmapheresis, 4.84 gm. per liter; after first red cell return, 4.66 gm. per liter; after second red cell return, 5.19 gm. per liter.

October 14: Blood urea nitrogen, 109.4 mg. in 100 c.c. Blood chlorids, 5.31 gm. per liter.

October 15: Yesterday and today the patient has been much more drowsy than previously and today he has taken little nourishment. His systolic blood pressure, previously from 200 to 220 mm. Hg, is now 270. There is no edema or ascites.

October 16: Patient has been comatose for the last twenty-four hours. Systolic blood pressure this afternoon, 290. Died at 12:15 a. m., October 17.

DISCUSSION

Plasmapheresis, in so far as it was carried in this case, has not arrested the march of uremia in any degree. The encouraging betterment which is noted early in the patient's stay in the hospital is no more than one often sees from rest and proper diet. Whether plasmapheresis can be carried to greater extent remains to be seen, but it seems improbable that real good can come from it in chronic cases with impending uremia. The other patients on whom we have used the maneuver have been of similar type and have received no benefit from it or from blood transfusion. It is possible that a case of acute nephritis with suppression of urine might be tided through a critical period of impending uremia by repeated plasma removals, but our series does not contain any such case.

It is of some interest to note that the urea nitrogen of the plasma increases slightly during the process of blood dilution. This finding corroborates that of Turner, Marshall and Lamson,² and cannot be explained without more complete studies on nitrogenous metabolism than we at present possess.

CONCLUSIONS

1. A method is described which permits repeated withdrawals of blood and return of washed cells without the use of herudin.
2. Plasmapheresis of this type has been carried out eighteen times in eight different cases of chronic nephritis and uremia without definite benefit to the patients.
3. It is suggested that the maneuver can have clinical value in no cases save those of acute suppression of urine where it is a question of tiding over a brief period.

POLIOMYELITIS, CLINICALLY ATYPICAL BECAUSE
OF COMPLICATING INFECTION BY A
PROTEUS-LIKE BACILLUS *

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Poliomyelitis, fortunately, has thus far been a disease of rare occurrence in the Army. Epidemic outbreaks probably will not occur, because of the immunity which most adults seem to have. Occasional cases may be expected to develop, especially in those who have just come from civil life, and unless they are recognized early and isolated, other cases may occur among the nonimmunes exposed by contact. A case of poliomyelitis contracted before arrival in camp was recently encountered at Camp Jackson, and the clinical course was complicated and the diagnosis rendered difficult by a secondary infection which was the result of the primary disease.

REPORT OF CASE

History.—The patient, an Italian laborer, was admitted to the Base Hospital, Camp Jackson, June 27, 1918, on his arrival from Chicago, complaining of indefinite pains in the left hip, thigh and knee. The temperature was 102 F. He was married, had no pernicious habits and denied venereal infection. His family history was negative. He gave a history of having received, in April, 1918, a blow in the left parietal region which rendered him unconscious. At the hospital to which he was taken he regained consciousness within twenty-four hours. A diagnosis of fractured skull was made from the roentgen-ray findings. He was later discharged from the hospital in an improved condition. He has since then never felt well, but at no time suffered from symptoms suggestive of a focal brain lesion.

Physical Examination.—Examination on admission determined a poorly nourished man, apparently 30 years of age, having a sickly appearance. The pupils were equal and reacted to light and accommodation. The tongue was slightly coated and tremulous. The pharynx was normal. Pyorrhea alveolaris was present. Slight enlargement of the cervical glands was noted. Examination of the heart and lungs was negative, except that the breath sounds had a harsh bronchovesicular quality over the right upper lobe anteriorly. The abdomen was rather full and prominent. No signs of fluid were present. Tenderness was elicited on deep pressure throughout, more marked in the right

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lower quadrant. The liver was not palpable and the spleen was easily felt 1 inch below the costal margin. The reflexes were found to be as follows: patellar absent, Achilles absent, plantar normal, deep reflexes of upper extremities active and equal; Romberg's sign was slightly present. Weakness of both lower extremities, the left greater than the right, was noted. Slight atrophy about the posterior part of the right hip joint was present. Tactile and pain sensation was found not impaired. The urine at the time of admission was reported normal and the white blood count was as follows: total 3,500; neutrophils 52 per cent.; small mononuclears 46 per cent.; eosinophils 2 per cent. Malaria organisms were not found. The diagnosis at that time was deferred. The general condition remained about the same for four days, the temperature remaining around 100 F., then subsiding to normal.

Clinical Course.—July 1 the abdomen was still markedly distended and increased weakness of both lower extremities was present. Atrophy of muscles of the left leg was noted. Standing unsupported was difficult and marked swaying of the body occurred when the eyes were closed. The blood Wassermann was reported negative and another white blood count on this date was as follows: total 3,000; small mononuclears 59 per cent., large mononuclears 3 per cent., neutrophils 38 per cent.

July 5. The patient appeared rather dull. Besides the findings previously noted, the liver was palpated two fingers' breadth below the costal margin and a doughy sensation was present on palpation of the distended abdomen. The temperature varied between normal and 100 F.

July 10. The patient looked chronically ill and complained of general abdominal pain. The tongue was coated and dry, the heart sounds were rapid, rate 100, of fair muscular quality and tone. No murmurs were present. The lungs presented no other definite signs except relative dullness at the bases posteriorly. The abdomen was moderately distended and tender on palpation all over, slightly more marked over the lower one-half. The sharp edge of the liver was palpated 1 inch below the costal margin. No masses were felt nor were signs of fluid present. The rectal findings were negative. The patient developed retention of urine and catheterization was necessary every eight hours or oftener. A surgical consultation was had and a diagnosis of tuberculous peritonitis was entertained. A white blood count on this date was: total 4,200; small mononuclears 25 per cent., large mononuclears 23 per cent., neutrophils 51 per cent., basophils 1 per cent. Malaria organisms were not found. The urine obtained by catheter was negative. The neurologic opinion was that a cord lesion involving the lower motor neuron was present, because of the rapidly advancing flaccidity and loss of muscle power in the lower extremities, occurring without sensory changes and with abolition of the deep reflexes.

July 12. The patient continued to run a temperature of about 100. He looked quite ill, was hyperesthetic and objected to examination. Voluntary movements of the legs were limited to feeble movement of the toes. The patellar and Achilles tendon reflexes remained absent. The neck was moderately stiff and slight weakness of the right face was noted. A tentative diagnosis of anterior poliomyelitis was made by Major W. W. Herrick and the patient was isolated. A lumbar puncture was performed and 8 c.c. of clear straw-colored spinal fluid was removed. This was reported as follows: Spontaneous coagulation in two hours; cell count 90 per c.mm.; small lymphocytes 99 per cent.; large lymphocytes 1 per cent.; globulin 4 plus. No organisms were found and the culture was negative. Wassermann was negative.

July 14. The temperature continued as before and eyeground examination without the use of a mydriatic showed the disk outline in the left eye indistinct with the veins slightly full and the arterioles standing out distinctly. No hemorrhage or exudate was present. The right eye was normal.

July 15. Thorough examination for the detection of hip joint and Pott's disease determined no evidence of these diseases present. Ear examination was also negative. No ova were found on feces examination.

July 16. Retention of urine as before noted continued to be present. Bowel movements were sluggish and enemas had to be given frequently. The appetite was poor. A blood culture which was taken on the 12th was reported on this date to be positive for meningococci, as proved by agglutination with polyvalent antimeningococcus serum. Active antimeningococcus treatment was started after another specimen of blood was taken for culture. The latter was subsequently reported negative. A total of 320 c.c. of antimeningococcus serum was given intravenously and 60 c.c. intraspinally in a period of three days. The spinal fluid while under treatment became quite clouded, was reported to contain many pus cells, but at no time were organisms found. While under treatment the patient's general condition improved markedly. He appeared brighter, developed fair appetite and was less complaining. Flaccidity of both lower extremities and distention of the abdomen remained, however, as before. A return of the power to void voluntarily and control the rectal sphincter was a surprising result of the serum therapy. This continued until July 20 when incontinence of urine and feces occurred.

July 18. The patient complained of pains shooting up and down both lower extremities. The serum treatment was discontinued on this date. The general condition was still improved.

July 19. The deep reflexes of the upper extremities were noted to be prompt and equal. The reflexes of the lower extremities remained absent. Tactile and pain sensation was not impaired. Eyeground examination determined no pathologic condition present. No choroid tubercles were found. The urine report on this date was as follows: Neutral, specific gravity 1.003, albumin trace, sugar negative, microscopic examination negative, heavy amorphous deposit present.

July 20. Roentgen-ray report of examination of head, entire vertebral column and chest was reported as follows: No evidence of fracture of skull or tuberculosis of the vertebral column. No infiltration of lungs present. The patient on this date began to do poorly. The temperature rose to 102 and remained irregular, varying between normal and 104 until death. Incontinence of urine with retention continued. Frequent involuntary bowel movements also occurred. Rectal examination determined the loss of the sphincter reflex. Absolute flaccid paralysis of both lower extremities was present. They were cold in comparison to the upper limbs. The abdominal reflexes were absent. The heart sounds showed nothing definite except impairment of muscular quality. The lungs were clear.

July 23. The white blood count was: total 3,200; small mononuclears 51 per cent.; eosinophils 4 per cent.; neutrophils 39 per cent.; basophils 1 per cent. The patient looked quite ill and presented the general features of a chronic illness. He had frequent desires to void, though the bladder was not full. The urine report was as follows: Cloudy, straw-colored, alkaline, specific gravity 1.004, albumin present, sugar negative, microscopic examination negative except for slight excess of epithelial cells.

July 26. The patient had a chill, and blood examination for malaria at that time was negative.

July 27. A lumbar puncture was performed and 30 c.c. of clear fluid was obtained under slight pressure. It was reported as containing 30 cells per c.mm., globulin 4 plus, no organisms, no tubercle bacilli, and the fluid was anticomplementary for the Wassermann reaction. Urine report of this date: cloudy, straw-colored, alkaline, specific gravity 1.000, albumin trace, sugar negative, microscopic examination negative.

July 29. The patient appeared very weak but did not complain of any pain. Sphincter control of the bladder and rectum was entirely absent. Pos-

teriorly over the bases of both lungs signs of congestion were noted. The patient became weaker and died on Aug. 1, 1918.

To summarize briefly, the case was one which presented (1) a rapidly developing flaccid paralysis of both lower extremities, with loss of control of the bladder and rectal sphincters, and without any sensory changes; (2) a terminal sepsis without characteristic blood changes of a sepsis, and urine which remained apparently normal; and (3) a spinal fluid suggestive from its cell count of poliomyelitis or tuberculous meningitis, but misleading because of the presence of xanthochromia and spontaneous coagulation which were suggestive of an old subdural hemorrhage, or brain or cord tumor.

Necropsy.—From the record of the necropsy, which was held fifteen hours after death, the following notes are taken:

The right pupil is contracted, the left is in middilatation. The legs and thighs are small, apparently because of atrophy of muscles. The abdomen is distended. Peritoneal, pleural and pericardial cavities are normal. The heart, lungs, liver, adrenals, and gastro-intestinal tract show nothing which deserves special mention.

The spleen is enlarged to between four and five times the normal size. The capsule is smooth and bluish red in color, and the organ feels firm. On section the cut surface is dark red in color and shows a number of opaque, yellowish white, round bodies, from 1 to 2 mm. in diameter. These are dry and friable and shell out readily from the surrounding tissue. The malpighian bodies are visible.

Each kidney is enlarged to almost double the normal size. The pelves are moderately distended and the ureters are 1 cm. in diameter. The surface of each kidney shows numerous slightly raised, nodular, opaque, grayish areas from 1 to 3 mm. in diameter, some of which are surrounded by areas of congestion. On section the cortex is thickened and is traversed by numerous, opaque, grayish streaks which end superficially in the areas noted on the surface. The pelves and ureters contain yellow, cloudy fluid.

The inner surface of the calvarium is normal and shows no evidence of previous fracture. The dura is not abnormally adherent to the bone. The inner surface of the dura over the left cerebral hemisphere is covered by a thin, rather firmly adherent layer of dark red material; over the parietal lobe this is yellowish in color. The pia is normal. There is a slightly increased amount of clear fluid in the sulci of the parietal lobes. The dura and pia of the base of the brain and the base of the skull appear normal. On section the brain appears normal.

The veins of the lumbar cord and of the cauda equina are markedly distended. The membranes of the cord are normal. On section the anterior horns of the gray matter of the lumbar cord stand out prominently, are pink in color, and appear to be softer than normal. The rest of the cord is normal on section.

Microscopic Examination.—The following notes are taken from the record of the microscopic examination:

Liver: The tissue contains numerous cellular islands, composed chiefly of lymphocytes. In these areas the liver cells are degenerated or necrotic or have disappeared completely; most of the islands are interlobular, but some are intralobular. There are a few small areas in which the liver cells are necrotic, but no cellular infiltration is present.

Spleen: The tissue is moderately congested. The opaque yellowish areas noted in the gross are composed of structureless, granular, eosin-stained material, which peripherally contains fine chromatin granules. Externally the mass is surrounded by compressed, congested spleen tissue.

Kidney: Scattered about in the cortex are irregularly shaped, poorly outlined cellular areas, composed chiefly of pus cells. In such areas some tubules and glomeruli are completely necrotic, other tubules are filled with pus cells,

and still others have disappeared completely. The tissue of the pelvis is diffusely infiltrated by pus cells.

Dura: The dura of the left cerebral hemisphere is normal, but beneath it is a layer of new formed tissue almost double the thickness of the dura. The fibers of this tissue are dense. The capillaries are wide and thin walled. In the tissue are numerous swollen, rounded and elongated cells which are filled with coarsely granular, dark brown pigment. Many well preserved red corpuscles are free between the fibers of the tissue. Just beneath the dura the tissue contains young fibroblast nuclei and a few lymphocytes.

Brain: The pia is edematous and contains moderate numbers of round and spindle cells which are filled with granular pigment which is not so dark as that present in similar cells in the tissue beneath the dura. The brain tissue is normal.

Cord: In the lumbar cord the ganglion cells of the anterior horns show varying degrees of degeneration. Some contain finely granular brown pigment and have no nuclei. Others contain numerous large, clear vacuoles. Still others are granular and completely broken up. Most of the cells which are better preserved contain large chromatin staining granules of the appearance and distribution of Nissl bodies. Lymphocytes in moderate numbers are present in both gray and white matter. Neurophagocytosis is not marked; an occasional degenerated ganglion cell is surrounded by a few lymphocytes. The capillaries of the anterior horns are moderately distended. In the pia, lymphocytes are fairly numerous, being especially aggregated about the blood vessels. In the cervical cord an occasional degenerated ganglion cell is present in the anterior horns.

Diagnosis.—The anatomic diagnosis summarizes the findings as follows: Subacute poliomyelitis of lumbar cord. Atrophy of muscle of lower extremities. Multiple abscesses of both kidneys. Bilateral pyoureter and pyonephrosis. Organizing subdural hemorrhage of left cerebral hemisphere. Chronic hemorrhagic pachymeningitis of left cerebral hemisphere. Acute splenic tumor. Cloudy swelling and multiple abscesses of liver.

Bacteriology.—Cultures were made from the hemorrhagic dura, the subpial fluid, the kidney abscesses, and the spleen. In all there developed a slender, motile bacillus, the cultural reactions of which were as follows:

Broth: In twenty-four hours, uniformly clouded, with no sediment or pellicle. In forty-eight hours a thin pellicle is formed.

Peptone Water: Growth is the same as in broth; no indol is formed.

Litmus Milk: Not changed in twenty-four hours. In forty-eight hours the medium is acid throughout and is peptonized at the surface. In seventy-two hours the litmus is almost completely decolorized and the upper fourth of the milk is peptonized. In five days, completely decolorized, almost completely peptonized, with a putrefactive odor.

Loeffler's Blood Serum: Partially liquefied in forty-eight hours, the liquefaction becoming complete later.

Dextrose Litmus Agar: Acid and gas in twenty-four hours. Gas increased in forty-eight hours, the butt partly decolorized. No further change later.

Maltose Litmus Agar: In twenty-four hours the butt is acid but no gas is formed. In forty-eight hours the butt is decolorized; no gas has been formed.

Lactose Litmus Agar: No change.

Saccharose Litmus Agar: No change in twenty-four hours. In forty-eight hours the butt is decolorized without gas formation.

Mannite Litmus Agar: No change.

Inulin Litmus Agar: Butt decolorized without gas formation in twenty-four hours; no further change later.

The organism appears to be a member of the proteus group, although the absence of coagulation of milk, of indol formation, and of saccharose fermentation is atypical for the usual strains of *B. proteus*.

DISCUSSION

The complicating infection, which made this case so puzzling clinically, was such a one as might be expected to occur with the spinal cord involvement situated where it was. Given paralysis of the bladder and rectum, with repeated catheterization and frequent involuntary defecation, and one rather expects ascending secondary infection of the urinary tract to occur. But the laboratory examinations, which should have cleared up this feature of the case, failed to do so, and there were added other features, some of which are difficult to explain. The involvement of the dura, the result of the injury to the skull three months before admission, was apparently without effect on the clinical complex on admission. The stiffness of the neck and weakness of the face which were noted on July 12 may have been the result of edema and perhaps of diffuse hemorrhage of the thickened dura. The cell count and globulin content of the spinal fluid suggested either poliomyelitis or tuberculous meningitis, but the pigmentation and spontaneous coagulation of the fluid were difficult to correlate with either possibility, and it remained for the necropsy to show that these confusing findings were due to the old subdural hemorrhage. Why the repeated urine examinations failed to detect the pus which must have been present in the urine and the detection of which would have cleared up the nature of the infection which overshadowed the later clinical picture, is difficult to explain except on the ground that the urine was always highly alkaline and that the pus cells may have undergone solution. The continued absence of leukocytosis after the secondary infection developed also helped to confuse the clinical picture, and is difficult to explain except on the basis of a lack of reactive power on the patient's part. The isolation, from blood taken on July 12, of a gram-negative diplococcus which was agglutinated by polyvalent antimeningococcus serum is a most puzzling phenomenon. The spinal fluid at this time was negative culturally, a similar organism could not be obtained at necropsy, and there was absolutely no postmortem evidence of previous localization of the meningococcus in the meninges. Possibly there may have been a blood invasion by the meningococcus, a feature of meningococcus infection the importance of which has been emphasized in the investigations of Major W. W. Herrick, chief of the medical service at this hospital. And this invasion may have yielded to the treatment with specific antiserum before there was any meningeal localization. At this stage the case was clinically one of poliomyelitis.

The temporary improvement in the general condition which followed the intravenous administration of antimeningococcus serum may have been a reaction of the nature of the nonspecific reaction which

follows the introduction of foreign protein in other acute infections. The transient amelioration of symptoms due to cord involvement, after intraspinal serum treatment, may have been the result of stimulation by the serum of only partially degenerated neurons. The case is instructive because of its puzzling features, some of which are difficult or impossible of explanation, and because it emphasizes the importance of not permitting too concentrated consideration of one feature of a case to overshadow other possibilities which may arise.

SUMMARY

A case of poliomyelitis, contracted by a soldier in civil life before his departure for camp, is described.

The earlier clinical course was that of an acute poliomyelitis involving the lumbar cord.

Xanthochromia and spontaneous coagulation of the spinal fluid were present, due to an old subdural hemorrhage which was the result of an injury three months before admission.

The later course was complicated by infection of the urinary tract and by generalized infection, the result of paralysis of the bladder caused by the poliomyelitis.

The organism which caused the secondary infection, while not a typical *B. proteus*, is apparently a member of the proteus group.

THE RELATIVE FREQUENCY IN RECRUITS WITH AND
WITHOUT THYROID ENLARGEMENT OF CERTAIN
SIGNS AND SYMPTOMS WHICH OCCUR IN
NEUROCIRCULATORY ASTHENIA *

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SECTION 1.—OBJECT OF THE INVESTIGATION

A considerable number of soldiers under training have been referred to the Cardiovascular Board on account of the presence of a syndrome which included all or most of the following signs and symptoms. The signs were increased pulse rate, tremor of the fingers and cold, moist hands which became cyanosed when dependent. The symptoms were precordial pain with dyspnea and palpitation on moderate exertion, such indications of vasomotor instability as dizziness, flushing and fainting, and a variety of other complaints, all pointing to a state of excessive reaction of the nervous system to psychic or physical strain.

It was the impression of the board that thyroid enlargement was almost constantly found in men with this syndrome. This fact raised the question as to the relationship between the thyroid anomaly and the development of these signs and symptoms. It was clear that they were not cases of exophthalmic goiter if for no other reason than that eye signs were not present. But it is known that in certain cases of endemic goiter a toxic state develops which resembles the condition we have outlined, and it has been shown in a previous report from the board that a high proportion of the men at Camp Lewis suffer from endemic goiter. It seemed possible, therefore, that the unwonted strain of military training had developed in these cases of endemic goiter an unusual number of instances of "toxic goiter." The possibility of holding such an opinion seemed further to be strengthened by the experience at Camp Upton where 75 per cent. of these men

* From the Cardiovascular Board, Camp Lewis, Wash. The statistics for this report were collected while the authors were members of the Cardiovascular Board.

were found to have thyroid enlargement. The condition is there attributed to hyperthyroidism.

But it will be noted that the supposition that an appreciable number of men with this syndrome were instances of "toxic goiter" was only tentatively held because of the impression that the condition was most commonly seen in men with thyroid enlargement. If this impression were a mistaken one there would be little reason for any such hypothesis, for on clinical grounds no distinction could be made between the syndrome in men with thyroid enlargement and those without it, and it seemed that there was a complete parallelism between the signs and symptoms we saw at Camp Lewis and those described under the term "Effort Syndrome" or "Neurocirculatory Asthenia" in England.

The object, therefore, of the survey here reported was to find whether or not the signs and symptoms we have mentioned were more frequent in recruits with thyroid enlargement than in those who had no thyroid enlargement.

SECTION II.—CONDITIONS UNDER WHICH THE FREQUENCY OF SIGNS AND SYMPTOMS IN THE TWO GROUPS WERE COMPARED

SUBSECTION A.—CLASSIFICATION OF RECRUITS INTO GROUPS

1. *Classification According to the Absence or Presence of Thyroid Enlargement.*—In some cases the existence of thyroid enlargement was not open to question. These men all had a swelling in the neck which was obvious on inspection and which moved on swallowing. These have been classed as "Certainly enlarged thyroids."

In other cases palpation during swallowing failed to reveal even the isthmus of the thyroid gland. These have been classed as "non-thyroids."

In still other cases, not inconsiderable in number, different observers might have disagreed as to whether or not thyroid enlargement were present. The isthmus was palpable, and in thin-necked individuals even visible. We are inclined to the view that in most of these cases the thyroid was enlarged beyond the limits of physiologic variation, but this was a point into which the element of judgment entered, and in a statistical study such as this in which a considerable mass of data was available, it seemed better to classify them separately as "Possibly enlarged thyroids."

2. *Classification According to the Origin of the Recruits from Districts where Endemic Goiter is Prevalent or Relatively Uncommon.*—So far as we know, there is no necessary correlation between the degree of thyroid enlargement and the occurrence or severity of the condition of toxic goiter. It is conceivable that in districts where

endemic goiter is prevalent a certain proportion of individuals may present more or less marked toxic symptoms, in whom there is no detectable or no obvious thyroid enlargement. Because of this possibility recruits free from any certain thyroid enlargement might not form a reliable normal standard for comparison with those in whom the thyroid enlargement was present, if they came from a district where endemic goiter was common. The normal standard, other things being equal, should be selected from districts free from endemic goiter. This was not possible since goiter is present in all the states from which recruits for Camp Lewis are drawn. But there are very marked differences in the frequency of the condition. Thus, only 8 per cent. of recruits from California had "possibly" or "certainly enlarged thyroids," while the percentage in Washington and Oregon was 39 per cent. and 32 per cent., respectively.

We have accordingly drawn a comparison between the incidence of signs and symptoms in recruits from California and in recruits from Washington and Oregon.

SUBSECTION B.—THE CONDITIONS OF EXAMINATION

A previous attempt to collect these data had shown that it was essential that the examination should be made before the men had received their first injection of typhoid vaccine, since that circumstance was in itself a sufficient cause for the development of some of the signs we were investigating. During the June draft, accordingly, an attempt was made to examine the men in the interval between the examination for communicable diseases and the injection of vaccine. This interval was short and was broken into to a considerable extent by the necessity of organizing the men in companies. As a result, data were obtained on only 314 men. These, however, were seen under satisfactory conditions, between 9 a. m. and 12 noon in their barracks. A squad room was filled with men who were directed to lie on their bunks flat on their backs without moving until they had been seen. No one was examined until they had lain quiet for at least five minutes.

During the July draft the investigation was greatly facilitated by a camp order under which the typhoid vaccination was postponed until the men were mustered in. Even then it was difficult, because of the absence of the men at the examining boards or the fitting of uniforms and the carrying out of preliminary drills, to see many men during the day, and the examination was therefore carried through between 6 p. m. and 9 p. m., after the men had been released from duty. The same plan of examining only after a period of complete rest in the recumbent position was followed.

SECTION III.—RELATIVE FREQUENCY OF CERTAIN ISOLATED
SIGNS IN RECRUITS WITH AND WITHOUT
THYROID ENLARGEMENT

SUBSECTION A.—INCREASED PULSE RATE

The pulse rate is determined by so many different factors that there can obviously be no generally applicable definition of what constitutes an increase over the normal in pulse rate. All that can be done is to determine the variability of the rate in normal individuals under certain arbitrary fixed conditions. The necessity for establishing some such standard, not only for the classification of cases dealt with in this report, but for more general use, has led to a separate study which will shortly be reported in detail. The basis chosen for this standard was the regulation hopping exercise test, but it was found necessary to modify this by preceding it by a period of rest in the recumbent position and by taking the first pulse count with the subject still lying down.

The average pulse rates under the conditions of this modified exercise test for the three groups of "Certainly enlarged thyroids," "Possibly enlarged thyroids" and "Nonthyroids" defined in Section II are given in Table 1.

TABLE 1.—AVERAGE PULSE RATES OF GROUPS OF RECRUITS CLASSIFIED
ACCORDING TO THE PRESENCE OR ABSENCE OF THYROID
ENLARGEMENT

Thyroid Enlargement	No. Recruits	Lying	Standing	After Hopping 100 Times	Two Min- utes After Hopping 100 Times
Certainly enlarged thyroids..	143	76	92	104	81
Possibly enlarged thyroids...	533	77	93	106	81
Nonthyroids	900	78	95	108	83

The figures in Table 1 show very definitely that thyroid enlargement in a group of individuals is not associated with any increase in the average pulse rate of the group, but it is still possible that in certain cases within the group the thyroid abnormality might have induced an increase in pulse rate, and that this increase might be of a distinctive nature, appearing, for example, to a greater degree in one or other of the different stages of the test. Those cases which showed abnormalities of pulse rate as determined by comparison with the pulse rate standard previously referred to, were therefore separated from the others and individually examined.

The number and percentage of the cases in each group presenting pulse rate abnormalities is given in Table 2.

The average pulse rate in the abnormal cases is given in Table 3.

It is not shown by either Table 1 or Table 2 that there is any characteristic difference in men who have abnormal pulse rates between those with and those without thyroid enlargement. This conclusion is

further supported by the results obtained when the deviations of each abnormal case from the standard are averaged. These are given in round figures in Table 4.

TABLE 2.—NUMBER AND PERCENTAGE OF RECRUITS WITH ABNORMALITIES OF PULSE RATE

Thyroid Enlargements	No. Recruits	No. Abnormalities	Percentage of Abnormality
Certainly enlarged thyroids.....	143	58	41
Possibly enlarged thyroids.....	533	194	36
Nonthyroids	900	372	41

TABLE 3.—AVERAGE PULSE RATES OF RECRUITS WITH ABNORMALITIES OF PULSE RATE

Thyroid Enlargement	Lying	Standing	After Hopping 100 Times	Two Minutes After Hopping 100 Times
Certainly enlarged thyroids.....	80	100	116	89
Possibly enlarged thyroids.....	83	103	118	90
Nonthyroids	84	104	119	91

TABLE 4.—AVERAGE EXCESS OVER THE STANDARD IN CASES WITH ABNORMALITIES OF PULSE RATE

Thyroid Enlargement	Lying	Standing	After Hopping 100 Times	Two Minutes After Hopping 100 Times
Certainly enlarged thyroids.....	7	7	11	5
Possibly enlarged thyroids.....	8	7	8	5
Nonthyroids	9	7	8	6

No importance can be attached to the deviation of eleven after hopping in the group of certainly enlarged thyroids, since this is the average of only sixteen men, one of whom showed an exceptionally high rate. There is then no indication that thyroid enlargement is associated with any special type of pulse rate.

The comparison between pulse rates of men from California and from Washington and Oregon where endemic goiter is most common, is vitiated by the fact that the average Californian rate was higher than the Washington and Oregon rate. It is because of the large number of Californians in the general nonthyroid group that the rate in the nonthyroid group of Table 1 is somewhat higher than the rates in the thyroid groups. The most accurate comparison is therefore between thyroids and nonthyroids coming from the same states. This is given in Tables 5 and 6.

It is apparent from Tables 5 and 6 that whenever a sufficiently large number of data are available the pulse rates are practically the same in both thyroid and nonthyroid groups. Nor is it possible to

detect any appreciable or constant difference in thyroid as compared with nonthyroid cases with abnormal pulse rates when the comparison is made between men from the same state.

TABLE 5.—AVERAGE PULSE RATES OF RECRUITS FROM WASHINGTON AND OREGON

Thyroid Enlargement	No. Recruits	Lying	Standing	After Hopping 100 Times	Two Min- utes After Hopping 100 Times
Certainly enlarged thyroids..	33	77	89	102	80
Possibly enlarged thyroids...	147	77	90	104	79
Nonthyroids	132	76	90	104	79

TABLE 6.—AVERAGE PULSE RATES OF RECRUITS FROM CALIFORNIA

Thyroid Enlargement	No. Recruits	Lying	Standing	After Hopping 100 Times	Two Min- utes After Hopping 100 Times
Certainly enlarged thyroids..	22	79	94	113	88
Possibly enlarged thyroids...	188	80	96	108	84
Nonthyroids	497	80	97	109	84

SUBSECTION B.—TREMOR

Tremor was defined as a fine shaking or unsteadiness of the fingers when the arm and hand were extended at right angles to the body. Only those cases were called positive in which the tremor involved all the fingers. Coarse, incoordinate movements of the whole hand or of individual fingers were not classed as tremors.

The number and percentage of tremors found in the three groups of recruits are given in the tables following.

TABLE 7.—NUMBER AND PERCENTAGE OF RECRUITS WITH TREMOR

Thyroid Enlargement	No. of Recruits	No. of Tremors	Percentage of Tremors
Certainly enlarged thyroids.....	143	44	31
Possibly enlarged thyroids.....	532	88	17
Nonthyroids	900	92	10

It would seem from Table 7 that there is a relation between thyroid enlargement and tremor, for tremor is three times more frequent in the group with certainly enlarged thyroids, and nearly two times more frequent in those with possibly enlarged thyroids, than in the nonthyroid group.

This association between thyroid enlargement and tremor is more evident when the comparison is confined to recruits from Washington and Oregon, the two states in which endemic goiter is most prevalent (Table 8).

In California, the state in which endemic goiter is least common, the percentage of tremor among the nonthyroid group is much higher. This may be connected with the fact that the majority of the Cali-

fornians were from cities (San Francisco, Los Angeles, Stockton, etc.), while nearly all the Washington and Oregon men were from the country districts.

TABLE 8.—NUMBER AND PERCENTAGE OF RECRUITS FROM WASHINGTON AND OREGON WITH TREMORS

Thyroid Enlargement	No. of Recruits	No. of Tremors	Percentage of Tremors
Certainly enlarged thyroids.....	33	5	15
Possibly enlarged thyroids.....	147	16	11
Nonthyroids	132	3	2

TABLE 9.—NUMBER AND PERCENTAGE OF TROOPS FROM CALIFORNIA WITH TREMOR

Thyroid Enlargement	No. of Recruits	No. of Tremors	Percentage of Tremors
Certainly enlarged thyroids.....	22	5	23
Possibly enlarged thyroids.....	188	19	10
Nonthyroids	497	47	9

The highest percentages of tremor were found in the June draft (Table 10).

TABLE 10.—NUMBER AND PERCENTAGE OF RECRUITS IN THE JUNE DRAFT WITH TREMOR

Thyroid Enlargement	No. of Recruits	No. of Tremors	Percentage of Tremors
Certainly enlarged thyroids.....	82	31	38
Possibly enlarged thyroids.....	150	44	29
Nonthyroids	181	33	18

The greater percentage in this group may possibly arise from an unconscious change in the standard adopted by the examiner as to what degree of unsteadiness should be termed "tremor." The fact remains that in every subdivision of the total number of men examined, those with certainly enlarged thyroids showed a relatively higher percentage of tremors than the nonthyroid group. This constant difference is sufficiently large to make it appear that a relation exists between enlargement of the thyroid gland and the occurrence of tremor.

SUBSECTION C.—CYANOSIS OF THE HANDS

The conditions under which examination was conducted were unfavorable for the detection of this sign. The previous experience of the Board in the examination of recruits with thyroid enlargement referred on account of cardiac symptoms had given rise to the impression that cyanosis of the hands was almost constant in such cases. These men were seen while they were standing, and the dependent position of the hands undoubtedly favored the delay in the circulation which is the cause of the cyanosis. But in this survey the men

had been lying for some time in bed with the arms in a horizontal position, and this doubtless is the reason why both in thyroid and nonthyroid cases the frequency of blue hands was so much smaller than that found in the comparison made between these groups in recruits of the May draft as they were in transit between examining boards. It was found that even when present it was not as a rule well marked and so much difficulty was experienced in deciding on border-line cases that it was decided after the June draft to postpone further inquiries into this point until more favorable conditions were obtained. The figures obtained during the June draft are given in Table 11.

TABLE 11.—NUMBER AND PERCENTAGE OF RECRUITS WITH
CYANOSIS OF THE HANDS

Thyroid Enlargement	Number Recruits	Number Cyanosed Hands	Percentage Cyanosed Hands
Certainly enlarged thyroids.....	82	15	18
Possibly enlarged thyroids.....	150	7	5
Nonthyroids	181	13	7

The numbers examined are too small to allow of any definite conclusion, though the larger percentage found in the group of certainly enlarged thyroids favors the hypothesis of a relationship between cyanosis of the hands and endemic goiter.

SUBSECTION D.—CURVED NAILS

By curved nails is meant an anteroposterior curving. A slight anteroposterior curve is extremely frequent in all individuals. It is commonly most marked in the nail of the index finger and becomes progressively less pronounced in the third, fourth and fifth finger nails. Only those cases were noted as having curved nails in which the fourth nail was very considerably curved. This is a more rigorous definition than was used in the comparison between thyroid and nonthyroid cases in the May draft and the figures are therefore not comparable.

The results obtained in the examination of the June draft are given in Table 12.

TABLE 12.—NUMBER AND PERCENTAGE OF RECRUITS WITH CURVED NAILS

Thyroid Enlargement	Number Recruits	Number Curved Nails	Percentage of Curved Nails
Certainly enlarged thyroids.....	82	25	31
Possibly enlarged thyroids.....	150	43	29
Nonthyroids	181	40	22

No further observations on this point were made, as it was felt that no certainty could be attained by purely statistical methods in regard to a matter in which it was so difficult even for the same

observer to maintain a constant standard. As in the case of cyanosis of the hands, a large proportion of the cases were only doubtfully classified.

To any one whose clinical work has been confined almost entirely to the inhabitants of cities, the cyanosis of the hands and curving of the finger nails seen in recruits is at first regarded as a definite and probably significant abnormality. But this impression goes when it is discovered how frequently these signs are found. It is believed, though no figures are available to test this impression, that the cyanosis is most frequent in recruits from the country, whose work has entailed much exposure of the hands to cold with a consequent gradual loss of vasomotor control and a condition of constant dilatation of the capillaries and small vessels so that when their hands are dependent there is a delay in the rate of flow of blood. It may be that the curving of the nails is a secondary result of this circulatory stasis.

The higher percentage of both cyanosis of the hands and curving of the nails in cases with certainly enlarged thyroids, suggests that there may be some association between enlargement of the thyroid gland and loss of vasomotor control in the vessels of the hands.

SUBSECTION E.—MOIST HANDS

By moist hands is meant any perceptible degree of moisture on the palm of the hand.

The significance of this sign of course varies with the condition of the examination. On a close, warm day it may be almost universal. But as the thyroid cases were well distributed throughout the whole group of men examined, the determination of the relative incidence of this sign was not thereby affected, though it is probable that if it had been possible to examine the men during cold dry weather more valuable results would have been obtained. A pronounced clamminess or wetness of the palms of the hands even when the air is cool and dry is certainly very frequent in men presenting the syndrome of neuro-circulatory asthenia. The results obtained in the examination of the June and July drafts are given in Table 13.

TABLE 13.—NUMBER AND PERCENTAGE OF RECRUITS WITH MOIST HANDS

Thyroid Enlargement	Number Recruits	Number Moist Hands	Percentage of Moist Hands
Certainly enlarged thyroids.....	143	99	69
Possibly enlarged thyroids.....	533	339	64
Nonthyroids	900	553	61

The relatively large number of men examined gives value to the differences noted in Table 13 even though they are not marked. It

is evident, however, from the high percentage of nonthyroid men with moist hands that the relation of thyroid enlargement to this sign, if it exists at all, must be very indirect. A comparison of the percentage of moist hands in recruits from California—a relatively thyroid-free state in which most of the men examined were inhabitants of cities—with the percentage from Washington and Oregon—states where endemic goiter is most common, and in which the men examined were practically all loggers or farmers—suggests that the place of origin or the character of work are factors in the development of this condition (Tables 14 and 15).

TABLE 14.—NUMBER AND PERCENTAGE OF RECRUITS FROM CALIFORNIA WITH MOIST HANDS

Thyroid Enlargement	Number Recruits	Number Moist Hands	Percentage of Moist Hands
Certainly enlarged thyroids.....	22	16	73
Possibly enlarged thyroids.....	188	127	68
Nonthyroids	497	300	60

TABLE 15.—NUMBER AND PERCENTAGE OF RECRUITS FROM WASHINGTON AND OREGON WITH MOIST HANDS

Thyroid Enlargement	Number Recruits	Number Moist Hands	Percentage of Moist Hands
Certainly enlarged thyroids.....	33	19	58
Possibly enlarged thyroids.....	146	83	57
Nonthyroids	132	67	51

SUBSECTION F.—DERMATOGRAPHIA

A centrifuge tube with a round, blunt, smooth end was drawn in as uniform a manner as possible over the chest. A minute or two later the skin was examined and if a well defined red line were seen the case was noted as presenting dermatographia. Only men of the June draft were examined (Table 16).

TABLE 16.—NUMBER AND PERCENTAGE OF RECRUITS WITH DERMATOGRAPHIA

Thyroid Enlargement	Number Recruits	Number of Cases with Derma- tographia	Percentage of Cases with Derma- tographia
Certainly enlarged thyroids.....	82	31	38
Possibly enlarged thyroids.....	150	59	39
Nonthyroids	181	58	32

Table 16 shows that with this rough and rather inaccurate method there was no marked difference in the incidence of dermatographia in the nonthyroid and thyroid groups.

SECTION IV.—THE RELATIVE FREQUENCY OF CERTAIN
SYMPTOMS IN RECRUITS WITH AND WITHOUT
THYROID ENLARGEMENT

The symptoms which were considered may be divided into three groups. Dyspnea, palpitation and precordial pain are classed as cardiac symptoms. Dizziness, flushing and fainting are taken as indications of vasomotor instability. Mental irritability, emotionalism, apprehensions, depression, excitability and exhaustion and "shakiness" after exertion or excitement were all grouped under the heading of nervous instability.

It was not possible in the time available to take a careful or exhaustive history. But the system which was followed probably tended to give too low rather than too high an estimate of the frequency of these symptoms. After examining for thyroid enlargement and for tremor and moist hands, the recruit was asked what occupation he followed. The question "You had no difficulty, so far as your health was concerned, in doing that work, had you?" was then put. If he answered "No" and his work were heavy, no further questions were asked, and the case was marked negative as regards symptoms. If the occupation were a light or sedentary one he was further asked whether he got much exercise outside of his work, whether he could do heavy work if necessary, whether he could run well, etc. These initial questions were all directed towards determining whether or not there was dyspnea on moderate exertion without putting the question directly. If it appeared that dyspnea on exertion was present, an endeavor was made to determine its degree and constancy, and its association with other symptoms. In those cases in which there was a clear history of dyspnea on moderate exertion and the recruit had without prompting complained of some symptoms such as pain round the heart, dizziness or "nervousness," it was found necessary to save time by asking directly as to the presence or absence of the other symptoms which were studied, though the precaution was taken of putting questions in the negative form. It was unfortunately not possible to separate the cases with thyroid enlargement into the two groups of certainly and possibly enlarged thyroids since there were only nine cases of large thyroids with symptoms, a number far too small to have any statistical significance.

The percentage of cases with any of these symptoms in recruits with and without thyroid enlargement is given in Table 17.

TABLE 17.—NUMBER AND PERCENTAGE OF RECRUITS WITH SYMPTOMS

Thyroid Enlargement	Number Recruits	Number with Symptoms	Percentage with Symptoms
All enlarged thyroids.....	444	40	9
Nonthyroids	719	63	9

In Table 18 is the percentage frequency of the cardiac symptoms of dyspnea, palpitation and precordial pain. Table 19 shows the relative frequency of vasomotor instability and Table 20 the frequency of the symptoms grouped under the term nervous instability.

TABLE 18.—PERCENTAGE OF RECRUITS WITH CARDIAC SYMPTOMS

Thyroid Enlargement	Dyspnea	Palpitation	Precordial Pain
All enlarged thyroids.....	8	8	6
Nonthyroids	8	8	6

TABLE 19.—PERCENTAGE OF RECRUITS WITH SYMPTOMS OF VASOMOTOR INSTABILITY

Thyroid enlargement	Dizziness	Flushing	Fainting
All enlarged thyroids.....	7	4	3
Nonthyroids	7	6	3

TABLE 20.—PERCENTAGE OF RECRUITS WITH SYMPTOMS OF NERVOUS INSTABILITY

Thyroid Enlargement	"Nervousness"
All enlarged thyroids.....	5
Nonthyroids	7

The tables show quite conclusively that these cardiac, vasomotor and nervous symptoms are no more frequent in recruits with thyroid enlargement. Similar comparisons were made on recruits coming from the same states and though the numbers examined were too small to make these data worth recording, they support the conclusion which must be drawn from the consideration of the combined figures.

SECTION V.—RELATIVE FREQUENCY IN RECRUITS WITH AND WITHOUT THYROID ENLARGEMENT OF A SYNDROME RESEMBLING THAT OF TOXIC GOITER OR OF NEUROCIRCULATORY ASTHENIA

In the preceding sections it has been shown that tremor and moisture of the hands are somewhat more common in recruits with thyroid enlargement than in those who are free from it. On the other hand, all the symptoms, and the most important single sign—increase of pulse rate—were equally distributed between the two groups.

But no consideration of isolated signs and symptoms can be so decisive as the direct determination of the incidence of the syndrome itself. For each one of these is seen in many other conditions besides toxic goiter or neurocirculatory asthenia. It is only in association with one another that they become of diagnostic value. It is therefore conceivable that even though the distribution of these signs and symptoms, each considered separately, were uniform in thyroid and non-thyroid cases, it might yet be found that the characteristic association

of signs and symptoms was seen only or chiefly in the group with thyroid enlargement. So far as the object of this survey is concerned, we must attach the more decisive importance to the determination of the percentage of cases in each group which may be regarded as presenting this particular association.

It would be erroneous to assign a uniform numerical value to each sign and symptom and to treat the data in a purely mathematical manner, even if the number of our observations were sufficiently large to allow of the determination of coefficients of correlation. For no rigid definition of what is meant by "association of signs and symptoms" can be given. Though there is something clearcut and definite in the clinical picture presented by toxic goiter or by neurocirculatory asthenia, regarded as a whole, yet in detail there is a confusion of many symptoms differing in kind and in degree, and there is no distinctive sign always present, if the thyroid enlargement and the increased pulse rate of toxic goiter be excepted. It seemed, therefore, more correct to adopt a system of selection which, though necessarily arbitrary, conforms with the general method of clinical diagnosis in placing more weight on certain sections of the evidence and less in others. Now one of the outstanding clinical features in both conditions, though this is more especially true of neurocirculatory asthenia, is the multiplicity of subjective complaints and the paucity or even absence of objective evidence. So it comes about that it is mainly on symptoms and not on signs that diagnosis rests. And the special characteristic of the symptoms is the wide field they cover. It is not only the cardiac or the vasomotor or the nervous system which is at fault, but all three together.

In accordance with these clinical facts the following system of selection was adopted. Association of symptoms alone was first considered. Those cases which presented three or more symptoms, one at least of which had to be indicative of cardiac, one of vasomotor, and one of nervous instability, were enumerated in both thyroid and non-thyroid groups and their relative incidence determined. Subsequently the percentage frequency of the signs in these selected cases was compared with their frequency in thyroid and nonthyroid cases in general, in order to determine the degree to which this symptom-complex was associated with increased pulse rate, tremor, etc.

The number and percentage of recruits with the foregoing association of symptoms are given in Table 21.

So far as the data in Table 21 go there appears to be as high a proportion of men in the nonthyroid as in the thyroid group who may be regarded as presenting the symptom-complex we have defined. But the numbers are so small that during the last two days of the July draft

an endeavor was made to supplement them by examinations carried out in the building where the examining boards are stationed. Two thousand three hundred and sixty-seven men were questioned as to the presence of symptoms. The men went by in single file and each was asked whether his "wind was good." If any complaint were made the recruit was detained for further questioning. If it appeared that there was true dyspnea on moderate exertion not due to such causes as asthma, bronchitis or organic heart disease, a detailed history as to the existence of the train of symptoms we have enumerated was taken. The speed at which the work had to be done probably led to a number of cases being missed, for the proportion of men with the syndrome was found to be only about half as great as in the barracks examination. It was uniform for both thyroid and nonthyroid cases, however, so that it is justifiable to combine both sets of observations. This has been done in Table 22.

TABLE 21.—NUMBER AND PERCENTAGE OF RECRUITS WITH SYMPTOMS OF CARDIAC, VASOMOTOR AND NERVOUS INSTABILITY

Thyroid Enlargement	Number Recruits	Number with Symptoms	Percentage with Symptoms
Enlarged thyroids	444	23	5.2
Nonthyroids	719	44	5.8

TABLE 22.—NUMBER AND PERCENTAGE OF RECRUITS WITH SYMPTOMS OF CARDIAC, VASOMOTOR AND NERVOUS INSTABILITY

Thyroid Enlargement	Number Recruits	Number with Symptoms	Percentage with Symptoms
Enlarged thyroids	1,346	51	3.8
Nonthyroids	2,184	86	3.9

The even distribution of the symptom-complex between thyroid and nonthyroid cases in this larger series seems to be a conclusive argument against the view that thyroid enlargement is concerned in the causation of the condition. Yet it is still possible that it may modify it, so that, for instance, certain symptoms may be found to occur with greater frequency when thyroid enlargement is present. Accordingly, the percentage frequency of the symptoms in cases with the syndrome is compared in Table 23.

TABLE 23.—PERCENTAGE OF SYMPTOMS IN RECRUITS WITH SYMPTOMS OF CARDIAC, VASOMOTOR AND NERVOUS INSTABILITY

	Cardiac			Vasomotor		Nervous	
	Dyspnea, Per Cent.	Palpi- tation, Per Cent.	Pre- cordial Pain, Per Cent.	Dizzi- ness, Per Cent.	Flush- ing, Per Cent.	Faint- ing, Per Cent.	Nervous- ness, Per Cent.
Enlarged thyroids...	100	96	82	96	65	45	100
Nonthyroids	100	96	86	96	84	46	100

Table 23 shows that the condition remains the same as regards symptoms irrespective of the presence or absence of thyroid enlargement. It is true that the percentage of complaints of flushing is higher in nonthyroid cases, but no great significance can be attached to such a difference because of the relatively small number of cases examined.

The data obtained in the examining building on the incidence of tremors and moist hands in cases with the symptom-complex are combined with the observations made in the barracks in Table 24.

TABLE 24.—PERCENTAGE OF TREMORS AND MOIST HANDS IN RECRUITS WITH SYMPTOMS OF CARDIAC, VASOMOTOR AND NERVOUS INSTABILITY

Thyroid Enlargement	Percentage of Tremors	Percentage of Moist Hands
Enlarged thyroids.....	49	90
Nonthyroids	30	73

Table 24 shows that these signs are especially associated with the symptom-complex. For the percentage of tremors was 19 per cent. in all thyroid cases, and 10 per cent. in all nonthyroids, as compared with 49 per cent. and 39 per cent. in the similar groups with the symptom-complex. These cases may therefore be regarded as presenting that particular combination of symptoms and signs of which the syndrome under discussion is composed.

It is noteworthy that the difference between the percentages of tremor in all thyroid and nonthyroid cases is relatively about the same as the corresponding difference in the percentages of those with symptoms. It would therefore appear that the difference in the group with symptoms is simply a reflection of a general difference between thyroid and nonthyroid cases, a difference which is quantitatively but not proportionately changed with the coincidence of the syndrome.

Unfortunately, it was not possible during the examinations in the examining building to take pulse counts in a manner uniform with the method adopted in the barracks, and the number of observations on this sign is therefore too small to be decisive.

Of the 23 thyroid cases with symptoms, 13, or 57 per cent., had some abnormality of the pulse rate as judged by our standard; while 19, or 45 per cent., of the 42 nonthyroid cases had increased pulse rates. This difference may well be accidental, for Table 25 shows that there is no appreciable difference between the average pulse rates either of all the cases or of those only which were abnormal.

In general, it would seem justifiable to conclude from the tables in this section that the incidence of the syndrome is relatively the same in thyroid and nonthyroid cases, that the distribution of symptoms is the same, and that such differences as are found in the percentage of

tremors and moist hands are not peculiar to recruits with the syndrome, but are also found in a comparison of all thyroid and nonthyroid cases.

TABLE 25.—AVERAGE PULSE RATES OF THYROID AND NONTHYROID CASES WITH SYMPTOMS OF CARDIAC, VASOMOTOR AND NERVOUS INSTABILITY

	All Cases with Syndrome				Cases with Abnormal Pulse Rate			
	Lying	Standing	Hopping	After	Lying	Standing	Hopping	After
Thyroid Enlargement								
Enlarged thyroids.....	83	101	118	90	85	105	127	93
Nonthyroids	85	103	119	90	90	108	127	95

SECTION VI.—SUMMARY

The immediate object of the survey was to find whether those signs and symptoms which occur in neurocirculatory asthenia, and which may also be present in toxic goiter, were more commonly seen in recruits with thyroid enlargement than in those who had no thyroid enlargement. The principle findings in regard to those points are summarized in Table 26.

TABLE 26.—SIGNS AND SYMPTOMS WITH AND WITHOUT THYROID ENLARGEMENT

Signs or Symptoms	Percentage With Thyroid Enlargement	Percentage Without Thyroid Enlargement
Increased pulse rate.....	37	41
Tremor	19	10
Cyanosis of hands.....	9	7
Curved nails.....	29	22
Moist hands.....	65	61
Dermatographia	39	32
Dyspnea on exertion.....	8	8
Palpitation	8	8
Precordial pain.....	6	6
Dizziness	7	7
Flushing	4	6
Fainting	3	3
Nervousness	5	7
Symptom-complex	4	4

There is no significant difference in the incidence of cases with increased pulse rate; but tremors, and to a lesser extent, moist hands, are somewhat more frequent in the thyroid than in the nonthyroid group. The number of men examined for cyanosis of the hands, curved nails and dermatographia is not sufficiently large to warrant any definite conclusion.

So far as symptoms are concerned it is apparent that there is no appreciable distinction between the two groups.

What has been termed the "symptom-complex," that is, an association in the same individual of symptoms of cardiac, vasomotor and nervous instability, is as often seen in nonthyroid as in thyroid cases.

Though all the details included in the immediate objective have not been adequately dealt with, yet there appears to be sufficient ground to serve as a basis for an opinion in regard to the larger question to answer which these data were gathered. It was to obtain evidence for or against the supposition that in cases with thyroid enlargement the thyroid anomaly was a direct or predisposing cause of these signs and symptoms that their frequency was compared in groups of recruits classified according to the presence or absence of thyroid enlargement.

The greater proportion of tremors in the thyroid cases must first be considered. In the case at least of tremors, reference to the detailed tables in Section III will show that this finding is so marked and so constant that it cannot be dismissed as accidental. Is it then justifiable to conclude that it is necessarily caused by the thyroid abnormality? Obviously not, for there are many other causes of tremor besides hyperthyroidism. The high percentage in recruits free from any suspicion of thyroid enlargement, and coming from California, the state where endemic goiter is least common, is sufficient to demonstrate this. It is at best an hypothesis whose acceptance or rejection will depend on the presence or absence of other indications of the state of hyperthyroidism found in toxic goiter. Now increased pulse rate is the distinctive clinical sign in toxic goiter. It is distinctive because it is the result of the underlying increase in rate of metabolism which is the fundamental difference between this condition and many others which superficially resemble it. For this reason the uniformity which was found in the pulse rate in thyroid and nonthyroid cases is of greater importance than the difference in the incidence of tremors, and makes it improbable that the enlarged thyroid gland in these cases was responsible for the greater incidence of tremors, or, indeed, was the cause of any other constitutional signs or symptoms.

But, as was pointed out in Section V, much more conclusive evidence is to be derived from a consideration of the relative frequency of cases with the symptom-complex than can be obtained from the incidence of isolated signs and symptoms. It has been shown that signs were considerably more frequent in the group of recruits with the symptom-complex than in all cases combined. Many of these men presented in a fully developed form the syndrome described in the introduction to this report; in all of them it was at least potentially present. If thyroid enlargement were a cause of this syndrome, we should certainly expect to find a large proportion of men with the symptom-complex in the thyroid group. But the distribution is the same in the thyroid and nonthyroid cases. On this ground it may be concluded that the development of toxic goiter is not the cause of the syndrome even in men with enlarged thyroids. The enlargement of the thyroid gland in such cases is incidental and not causative.

Since the thyroid has no demonstrable etiologic relationship to this syndrome, there is no reason why, provisionally at least, a diagnosis of neurocirculatory asthenia should not be made in all these cases. Nor is there any reason why cases of thyroid enlargement with the syndrome should be considered as in any essential respect different from those without thyroid enlargement, nor any reason why the treatment and the disposition of these cases should necessarily be altered by the thyroid enlargement as such.

The starting point of this work was the impression that thyroid enlargement was almost constantly present in cases with the syndrome. This impression has not been confirmed. To some extent it was probably erroneous. But it should be remembered that it was obtained from examinations, not of recruits, but of soldiers who had been for some months at Camp Lewis. In the course of a correspondence on this subject, Dr. H. S. Plummer said that he was convinced that thyroid enlargement was more prone to occur in cases of neurocirculatory asthenia than in normal individuals. Since Camp Lewis is situated in a district where endemic goiter is extremely prevalent, it may be that some of these soldiers with neurocirculatory asthenia developed thyroid enlargement only during their stay in camp. Undoubted instances of the new development of goiter in normal individuals stationed at Camp Lewis have been noted.

STUDIES OF THE CHEMISTRY OF PERNICIOUS ANEMIA *

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Squier¹ has written an interesting and comprehensive review of the literature on the chemistry of pernicious anemia. Though a number of researches have been made on the pathochemistry of this very fatal disease, its causative factor is still unknown. Whether it is essentially a disease of the gastro-intestinal tract, with atrophy of the gastric mucosa and the absorption either of enterogenous poisons or protein split products, or whether it is a disturbance due to the hemolytic action of toxins elaborated in disease processes, or whether the disease is caused by hypersplenism, are the three main hypotheses in this mooted question.

The evidence brought forward by those authors who favor one or the other of these theories is not conclusive. A large number of chemical substances, such as oleic acid, saponins, phenylhydrazin, b-aminq-azolyl-ethyl benzaldehyd, p-oxyphenylethylamin, etc., are violent hemolytic agents, and experimentally such poisons will produce anemia and hemoglobinuria, etc., but no definite proofs have been advanced that such substances are actually present in the idiopathic anemias. Iwao has been able to isolate p-oxyphenylethylamin from autolyzing pancreas, putrefying horse flesh and Swiss cheese. It is quite evident that this base may normally arise in the intestine from putrefying food, and it has been demonstrated by Berthelot and Bertrand² that there is an organism in the intestine—*B. aminophilus*—which can produce p-oxyphenylethylamin from tyrosin. Barger and Dale³ have isolated another hemolytic amin, b-imino-azolethylamin, from the mucosa of the small intestine of the ox. Grawitz⁴ assumed that intestinal stasis was a great cause in the production of pernicious anemia, due to the absorption of poisons from the decay of food in the alimentary canal. Berger and Tsuchiya⁵ found that extracts obtained from the mucosa of the intestines of anemic animals have a much stronger hemolytic power than extracts from the mucosa of normal animals. This has, however, been controverted by Ewald and Friedberger.

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1. For complete bibliography see Squier, T. L.: J. Lab. & Clin. Med. 2: No. 8, 1917.

2. Berthelot and Bertrand: Compt. rend. Acad. Sc. 154:1463, 1912.

3. Barger and Dale: J. Physiol. 61:499, 1911.

4. Grawitz: Berl. klin. Wchnschr., 1898, pp. 704, 730.

5. Berger and Tsuchiya: Arch. f. klin. Med. 94:252, 1908.

McPhedran found that the hemolytic power of organ extracts of cases of pernicious anemia fell entirely within normal limits, and gave no evidence of the presence of hemolytic toxins supposed to be the causative factor of the disease. That the lipin metabolism may be disturbed in the idiopathic anemias has been surmised by a number of authors. Kinnicutt reports two cases of pernicious anemia, which at necropsy showed lipoidosis of the adrenal cortex. This was indirectly and directly confirmed by the investigations of Hueck⁶ and of Landau.

It has been thought by Moffitt that hypersplenism as a cause of this disease may be brought about by toxins which reach the spleen through the main splenic arterial blood supply. "Erythrolysis does not take place in the spleen, but in some way the erythrocytes are sensitized and prepared for later destruction in the liver, marrow or lymph glands."

Examination of the Blood.—The bloods of three patients suffering from pernicious anemia were examined for certain constituents, and the results recorded (Table 1). We shall discuss several of the items individually. We have confirmed the findings of Ruttan and Adami (1896) that the specific gravity of the blood serum is lowered, that the total serum protein is much reduced—about 30 to 40 per cent.—and that the ash was somewhat increased. The calcium in the blood was above normal. The glucose and cholesterol of the blood were normal as well as the total fat content. In this regard we cannot corroborate King's results who found a high blood fat content and a reduced cholesterol content in cases of pernicious anemia.

Study of the Functional Capacity of the Gastro-Intestinal Tract.—The method suggested by Rehfuss for the fractional analysis of the gastric contents was applied, the residuum removed and examined, with the results marked in Table 2. The patients had fasted sixteen hours, from 6 p. m. to 10 a. m.

The residua seem to show a gastric stasis. According to Rehfuss, Bergeim and Hawk the volume of the normal average residuum is about 50 c.c., and shows a total acidity of about 30 and a free acidity of 18.5. In these cases the total acidity averaged 51, whereas the free acid was 0. It may be stated that no pepsin hydrochloric acid was found in the cases of pernicious anemia, while tryptic digestion was present showing a regurgitation of the duodenal contents. The removal of the samples of gastric contents after an Ewald test meal yielded the results in Table 3.

6. Hueck: See Squier, Footnote 1.

TABLE 1.—BLOOD ANALYSIS IN CASES OF PERNICIOUS ANEMIA

	Case 1	Case 2	Case 3
Specific gravity of serum.....	1.0272	1.0263	1.0259
Water content of blood, parts per thousand.....	856.12	843.27	839.75
Dry matter of blood, parts per thousand.....	143.88	150.73	160.25
Proteins of serum, parts per thousand.....	5.915	5.217	5.337
Fat, parts per thousand.....	5.05	4.2	4.4
Cholesterol, mg. per 100 c.c. blood.....	135.0	161.0	155.0
Nonprotein nitrogen, mg. per 100 c.c. blood.....	33.5	29.3	30.2
Urea nitrogen, mg. per 100 c.c. blood.....	20.1	18.4	19.7
Creatinin, mg. per 100 c.c. blood.....	2.8	4.8	5.4
Glucose, mg. per 100 c.c. blood.....	0.11	0.08	0.09
Uric acid, mg. per 100 c.c. blood.....	2.2	1.7	3.1
Carbon dioxide, parts per thousand.....	40.0	45.0	38.0
Ash, parts per thousand.....	0.77	0.82	0.85
Calcium oxid, parts per thousand.....	0.06	0.087	0.092
Hydrogen-ion concentration* (P _H).....	7.2	7.3	7.25

* Oxalated blood.

TABLE 2.—ANALYSIS OF GASTRIC RESIDUUM

Case	Volume, C.c.	Total Acid	Free Acid	Pepsin HCl	Trypsin	Bile
1	75	48	0	—	+	Present
2	58	65	0	—	+	—
3	64	40	0	?	+	—

The gastric curves produced by these cases of pernicious anemia strikingly resemble the curves of carcinoma of the stomach. The free acid is absent and the total acid varies between 15 and 45. No blood was present; a trace of lactic acid was found in Case 2; pepsin was absent. The gastric mucosa appears to be altogether nonfunctionating, due to the complete atrophy that is doubtless present of the mucous membrane. The patients (Cases 1 and 2) were complaining of gastric distress, belching and anorexia, and they stated that they felt better when a solution of hydrochloric acid and pepsin was administered to them.

A roentgenogram of the gastro-intestinal tract did not reveal any abnormalities.

The Gastro-albumorrhea test, as devised by Salomon and as modified by Wolff and Junghans, was applied in Cases 2 and 3. The total nitrogen in 100 c.c. of gastric contents was 4.1 mg. (Case 2) and

3.7 mg. (Case 3). No albumin was present as determined by the phosphotungstic acid precipitation method. It is to be assumed that there is no discharge of protein from the gastric mucosa, although there no doubt is a chronic inflammatory process, in quantities sufficient to be tested.

The intestinal digestion was then investigated by the method of Schmidt and Strassburger. The patients were put on the test diet for three days, and the feces, the daily amounts being marked off by carmin, were collected and examined.

TABLE 3.—FRACTIONAL ANALYSIS OF GASTRIC CONTENTS

Time, Minutes	Case 1		Case 2		Case 3	
	Free Acid	Total Acid	Free Acid	Total Acid	Free Acid	Total Acid
15	0	36	0	22	0	14
30	0	28	0	24	0	20
45	0	40	0	35	0	25
60	0	26	0	40	0	30
75	0	30	0	45	0	32
90	0	52	0	45	0	32
105	0	56	0	50	0	36
120	0	32	0	52	0	38
135	0	36	0	50	0	40
150	0	36	0	48	0	44
Blood.....	—	—	—	—	—	—
Lactic acid.....	—	—	Trace	—	—	—
Bile.....	—	—	—	—	—	—
Mucus.....	Normal	—	Much	—	Moderate	—
Food.....	Poorly digested	—	Poorly digested	—	Poorly digested	—
Pepsin.....	—	—	—	—	?	—

In a series of six healthy individuals placed on this test diet for three days, Schmidt found the average weight of the dry feces to be 54.3 gm. The maximum was 62 gm. and the minimum was 45 gm. In a case of pancreatic disease, Pratt found the weight of the feces to be above 400 gm. The average weight of the dry feces in five cases of "fermentative dyspepsia," Schmidt found to be 127.4 gm.; the average weight in "gastrogenous diarrhea" with achylia was 98.9 gm.

The analyses of the feces in three cases of pernicious anemia are given in Table 4.

TABLE 4.—ANALYSIS OF FECES AFTER SCHMIDT-STRASSBURGER TEST DIET

Case	Day	Weight Dry Feces, Gm.	Total Nitrogen		Fat	
			Gm.	Per Cent. of Intake	Gm.	Per Cent. of Intake
1	1	157.5	2.343	14.2	4.51	4.8
	2	162.4	2.544	15.4	6.05	5.5
	3	175.5	1.897	11.5	5.72	5.2
	Aver.	165.1	2.261	13.7	5.42	5.0
2	1	93.3	1.669	9.7	6.71	6.1
	2	75.5	1.026	11.2	4.29	3.9
	3	108.2	1.857	10.8	5.28	4.8
	Aver.	91.0	1.817	10.5	5.42	4.9
3	1	117.0	1.144	7.2	4.62	4.2
	2	110.5	1.033	6.5	3.96	3.6
	3	86.5	1.319	8.3	4.84	4.4
	Aver.	104.6	1.132	7.3	4.47	4.06

In our series of cases of pernicious anemia the bulk of feces was very much increased, from 75.5 gm. to 175.5 gm. It will be seen that the average daily excretion of dry feces in the three cases was 165.1, 114.0 and 104.6 gm., respectively, an increase of from 100 to 200 per cent. as compared with the normal figures of Schmidt. The nitrogen elimination was also much increased in the first and second cases, being an evidence of some deficiency of protein absorption. The average excretion of nitrogen in the feces in the three cases was 13.7, 10.5 and 7.3 per cent., respectively. The fecal fat does not seem to vary much from the normal, the average figures for the three cases being 5.0, 4.9 and 4.06 per cent., respectively.

Perhaps as index of *intestinal putrefaction* attention may be paid to the urinary sulphur partition. It is known that in cases of intestinal stasis, etc., where the flora of the intestines are abnormal, there is an increased production of aryl compounds which are conjugated in the liver with sulphuric and glycuronic acids, and are excreted in the urine. Normally, the ethereal sulphates form approximately 10 per cent. of the total urinary sulphur. We found, as shown in Table 5, that in the first two cases there was a marked increase in the percentage of ethereal sulphates eliminated, whereas in Case 3, the increase is only slight. To our mind this is a distinct evidence of some putrefactive change going on in the body. We are aware of the theory that a certain portion of the ethereal sulphates is of endogenous origin. Our experience has, however, led us to the conclusion that when marked quantities of ethereal sulphates are

excreted in the urine, presumptive evidence is present of intestinal putrefaction.

It will be noticed that the neutral sulphur fraction is also abnormally high, especially in Case 3, an evidence of body suboxidation.

TABLE 5.—URINARY SULPHUR PARTITION *

Case	Day	Volume Urine, O.c.	Total S, Gm.	Inorganic SO ₄		Etheral SO ₄		Neutral S	
				Gm.	Per Cent.	Gm.	Per Cent.	Gm.	Per Cent.
1	A†	1,470	1.892	1.1162	59	0.4351	23	0.3407	18
	B†	1,215	1.536	0.8448	55	0.3993	26	0.2919	19
2	A	1,625	1.074	0.5155	48	0.3014	29	0.2571	23
	B	1,780	1.139	0.6150	54	0.3075	27	0.2165	19
3	A	950	0.935	0.5797	62	0.1496	16	0.2057	22
	B	1,075	1.208	0.7006	58	0.1691	14	0.3383	28

* The total sulphur was determined by Benedict's method, and the inorganic and etheral sulphates by the method of Folin.

† The days were not successive.

Function of the Pancreas.—An Einhorn duodenal tube was passed on each of the patients and allowed to remain in the patient over night. In the morning the *duodenal contents* were removed and analyzed. We were successful in obtaining bile stained duodenal contents in each instance.

It was found that the pancreatic enzymes were present in abundance. Protease, amylase, and lipase were found in normal quantities. No blood was found in any of the specimens. The methods used were, that of Gross for trypsin, that of Wohlgemuth for amylopsin, and the milk-litmus test for lipase.

In this connection it may be stated that the result of the Schmidt-Strassburger test may be taken as evidence of the nonexistence of any pancreatic deficiency.

The *stools* obtained after the Schmidt-Strassburger diet were examined for the pancreatic enzymes and for blood, besides the usual examination for parasites, food particles, etc.

The pancreatic enzymes were present in abundance—trypsin, amylopsin and steapsin. No blood was found. No ova or parasites were found. Many meat fibers were, however, noticed. No free fat was observed.

The mucus in the stools varied. In one case the mucus was in abundance (Case 1); the other cases were normal.

The *blood* and the *urine* were examined for *amylase*, as suggested by Wohlgemuth, and by Wohlgemuth and Noguchi, as a test for pancreatic insufficiency. We can only report negative results.

The pancreas seems to be functioning entirely normally, as evidenced by the tests enumerated.

Study of the Liver Function.—Bauer's galactose test and Strauss' levulose test were applied in two of the cases, with results that were negative in both instances.

Bauer's galactose test is performed as follows:

Thirty gm. of galactose are administered to the patient in the morning, and the urine collected for the next five or six hours. The presence or absence of galactose in the urine is determined by the Fehling test. The levulose test is applied as follows: One hundred gm. of levulose are administered in the morning, and the urine voided during the following five or six hours, tested by the Fehling and Seliwanoff tests for the presence or absence of levulose.

*Sulpho-Conjugation Test.*⁷—It was demonstrated by Baumann and others that the toxic carbocyclic radicals split off from the proteins by the growth of intestinal bacteria are conjugated in the liver with sulphuric acid and thus detoxicated. It is also known that a portion of these aryl compounds are detoxicated by conjugation with glycuronic acid.

It is obvious that in testing for the functional capacity of the liver it is essential not only to test the glycogenic, ureogenic, biligenic, etc., functions, but also to examine the detoxicating power of the hepatic tissue in order to ascertain the complete working power of the gland. This is done in the following manner:

The patient receives a dose of castor oil to evacuate his bowels. He is then kept on a known diet for two days, during which time the urine is collected, preserved and analyzed for total sulphur and ethereal sulphates. On the third day the patient receives a capsule containing 0.5 gm. thymol. The urine is collected for the next two days, preserved, and again analyzed for total sulphur and for ethereal sulphates.

If all the thymol were absorbed, and if all the thymol were conjugated with sulphuric acid and none with glycuronic acid, the 0.5 gm. thymol would be excreted as 0.766 gm. of thymol sulphuric acid. This would cause a marked increase in the percentage of ethereal sulphates in the urine. If the detoxicating power of the liver were below par, the thymol would not be conjugated, and the percentage of ethereal sulphates would be only slightly different from what it had been on the first two days—before the thymol administration.

We have found that this detoxicating function of the liver usually runs parallel with the other functional derangements of this organ.

⁷ 7. Kahn, M.: Am. J. M. Sc. 155:668, 1918.

In some cases, however, the conjugating power of the gland is markedly reduced, whereas the other functions do not show any disturbances as determined by the methods at our disposal. In still other cases the sulpho-conjugation is entirely normal (as determined by the test here described), while the other tests show a reduction of hepatic functional capacity.

It will be seen from the results charted in Table 6 that there seems to be a deficiency in the detoxication function of the liver. While it is seen from the sulphur partition (Table 5) that the liver conjugates an increased amount of aromatic radicals as evidenced by the ethereal sulphate output, still the administration of an additional aryl compound, thymol, does not seem to call forth the proper detoxicating influence of the liver in sufficient force.

TABLE 6.—SULPHO-CONJUGATION TEST OF HEPATIC FUNCTION

Case	Total Sulphur, Gm.		Ethereal Sulphate Sulphur, Gm.		Ethereal Sulphate Sulphur, per Cent. of Total Sulphur	
	Before*	After	Before	After	Before	After
X†	2.0875	2.1295	0.2893	0.5646	14.2	26.8
1	1.536	1.6205	0.3993	0.5055	26.0	31.2
2	1.139	1.0974	0.3075	0.3237	27.0	29.5
3	1.208	1.1522	0.1691	0.2154	14.0	18.7

* Before the administration of thymol, and after.
† This was a normal individual.

Study of the Bile Pigments.—As Squier¹ says, where active erythrocyte destruction is taking place, it is natural to expect that the limit must be approached above which the liver can no longer dispose of the liberated pigment. That such actually is the case has been shown by Sellards and Minot. They found that, compared with normal, less hemoglobin is required to produce hemoglobinuria in patients suffering from pernicious anemia. The amount of hemoglobin necessary to induce hemoglobinuria bears no relation to the red cell count, but is in direct proportion to the amount of blood destruction taking place. This last, providing complicating factors are absent, is directly proportional to the excretion of urobilin in the intestine. Eppinger found that the normal urobilinogen excretion was 0.12 to 0.15 gm. per day. Schneider⁷ estimated the amount of hemolysis by examination of the duodenal contents and found in pernicious anemia, excessive excretion of bile pigments, or pleochromie, and urobilinocholia. Pleochromie is an expression of immediate hemolysis, and which, in pernicious anemia, whether in crisis or remission, is a constant finding. Urobilinocholia indicates a heaping

up of pigment in the portal system and varies directly as the portal system is surcharged or becomes relatively empty of the excess of pigment. Schneider⁸ points out that in secondary anemia no pleochromie or urobilinocholia is present (Squier¹).

We followed Schneider's technic in detail. The duodenal contents were collected and examined for the pigments as follows:

To determine bilirubin: To 10 c.c. of duodenal contents are added 10 c.c. of an alkaline solution of calcium chlorid. After vigorous shaking this is filtered. The precipitate is dissolved under gentle heat in 10 c.c. of acid alcohol and the resulting green solution concentrated to a given volume. By colorimetric comparison with a standard green solution, the quantity is indicated as +, ++, or +++.

To determine urobilin and urobilinogen: To 10 c.c. of duodenal contents are added 10 c.c. of Schlessinger's solution, the whole thoroughly shaken and allowed to filter. The filtrate should be slightly alkaline; if not, a drop or two of a weak ammonia solution are added. The filtrate will in the presence of urobilin show a more or less pronounced green opalescence. To 10 c.c. of this filtrate are added 1 c.c. of Ehrlich's benzaldehyd solution.⁹ In the presence of urobilinogen a red color will develop. This is allowed to stand in a dark place for fifteen minutes, and is then examined by the spectroscope (Schneider).

TABLE 7.—BILIARY PIGMENTS

Cases	Duodenal Contents			Urine		Feces
	Bilirubin	Urobilin	Urobilinogen	Bilirubin	Urobilin	Urobilinogen
Schneider's						
1	+++	+++	+++	0	+	
2	+++	2,000	1,600			
3	+++	4,000	2,800	0	1,000	
4	+++	2,000	1,200	0	1,000	+++
5*	+++	2,300	2,500	..	1,000	+++
Authors'						
1	+++	+++	+++	0	+	+++
2	+++	+++	+++	0	+	+++
3	+++	+++	+++	0	+	+++

* Urobilinogen in urine 100.

We applied these tests qualitatively and confirm Schneider's results (Table 8).

An examination of the *urinary nitrogen partition* was made in each case. In general the results were negative except that the oxyproteic acid nitrogen fraction was increased to twice the normal, a condition frequently met with in carcinoma and in syphilis. The results will be found in Table 8.

8. Schneider: Arch. Int. Med. 17:32, 1916.

9. Para-dimethylaminobenzaldehyd, 2 gm.; acid hydrochloric, 15 c.c.; water, 15 c.c.

TABLE 8.—URINARY NITROGEN PARTITION

Case	Volume, C.c.	Total N. Gm.	Urea N, per Cent.	Am- monia N, per Cent.	Uric Acid N, per Cent.	Purin N, per Cent.	Creat- inin N, per Cent.	Oxy- Protein N, per Cent.	Rest N, per Cent.
1	1,470	16.52	79.3	4.2	2.7	2.1	2.8	3.9	5.0
2	1,625	9.35	81.6	3.7	3.1	2.7	3.1	4.2	1.6
3	950	12.17	82.5	3.4	2.9	2.5	2.6	5.3	0.8

Study of Kidney Function.—The phenolsulphonephthalein test was tried twice on each case. The results, in general, did not indicate any deviation from the normal. It is always advisable, when one obtains a low phenolsulphonephthalein output to repeat the test for confirmation; for, we have found in numerous instances that a low output may only indicate a faulty technic rather than a poor renal function. Table 9 shows the results obtained in the three cases.

TABLE 9.—PHENOLSULPHONEPHTHALEIN OUTPUT

Case	Test Number	Per Cent. First Hour	Per Cent. Second Hour	Per Cent. Total
1	1	25	15	40
	2	48	40	88
2	1	37	30	67
	2	35	34	69
3	1	42	30	72
	2	40	28	68

Examination of the *blood plasma for several nitrogen fractions* (Table 1) showed that there was no increase in the nonprotein nitrogen, urea nitrogen, or uric acid. This is a good evidence of normal kidney function.

The only nitrogen fraction increased in the blood, especially in Cases 2 and 3, is the creatinin, due more to the destructive process present in the body rather than to any failure of the kidney to eliminate this substance. It is remarkable how often syphilitic patients yield a high creatinin figure in the blood.

There was acidosis, to a certain degree, present in all of the three cases of pernicious anemia. The carbon dioxid combining power of the plasma was much reduced, as determined by the Van Slyke method. The H ion concentration is increased, and the carbon dioxid of the alveolar air was 4.4, 4.7, and 4.6 in the three cases, respectively.

HISTORY OF THE CASES

CASE 1.—Jewish woman, 45 years old, married; no children; four miscarriages; husband well. A Wassermann¹⁰ was performed on her and twice found positive weakly. When she came to the hospital, she had a red blood count of 720,000, hemoglobin 35 per cent., color index 2, white blood count 6,600, neutrophils 53 per cent., eosinophils 1 per cent., large mononuclears 2 per cent., lymphocytes 44 per cent. There was marked anisocytosis and poikilocytosis. The coagulation time was 12.5 minutes; blood platelets 150,000. She remained in the hospital for three months, being transfused a number of times by the citrate method. Salvarsan had no effect. During one of the remissions she left the hospital.

CASE 2.—Married salesman; has one child; ill eight months; denies syphilis; had gonorrhea; Wassermann doubtful. Blood: red blood count 1,200,000, hemoglobin 45 per cent., color index 1.8; marked anisocytosis and poikilocytosis; normoblasts present; platelets 185,000; coagulation time 11 minutes.¹¹ The patient was transfused several times, but did not rally, and died. No necropsy.

CASE 3.—Married woman, aged 42; two children; ill one year. Blood: Wassermann negative; red blood count 1,400,000, hemoglobin 42 per cent., color index 1.3, blood platelets 210,000, coagulation time 13.5 minutes; white blood count 7,200, polynuclears 62 per cent.; many normoblasts. The patient was transfused several times, but left the hospital during a remission.

CONCLUSIONS

1. A study of the chemistry of three cases of pernicious anemia is presented.

2. The blood analysis shows a lessened specific gravity of the serum, reduction of the protein content, an increase in the ash and lime content, and a normal fat, cholesterol and glucose percentage.

3. There is complete anacidity present in the stomach, an increased residuum, and absence of pepsin, resembling the gastric picture present in cases of carcinoma ventriculi.

4. The Wolff-Junghans test is negative.

5. Intestinal digestion is disturbed. The fecal bulk is much increased, and the nitrogen lost in the feces above normal. The fat in the feces is normal.

6. Intestinal putrefaction, as evidenced by increased ethereal sulphate output, is present. There is a state of suboxidation—the neutral sulphur fraction is increased.

7. The pancreas functionates normally, as evidenced by enzyme examination of duodenal contents and feces.

10. It has been the experience of one of us (Kalm) that pernicious anemia patients very frequently have a positive Wassermann test.

11. The coagulation time was determined by collecting a few drops of blood from an arm vein by means of a needle into a flat bottom test tube. By gently tilting the tube occasionally, one can determine the coagulation time very exactly.

8. There is a deficiency in the hepatic detoxication function as shown by the sulphoconjugation test. The glycogenic and ureogenic functions of the liver are normal.

9. The excessive hemolysis of pernicious anemia is attended by both a pleochromie and a urobilinochole. In this regard we corroborate Schneider's experiments.

10. There is an increased elimination of oxyproteic acid nitrogen in the urine in cases of pernicious anemia; the other urinary nitrogen fractions being normal.

11. The renal function is normal as evidenced by the phenolsulphonephthalein test, and the blood nitrogen partition.

12. The creatinin in the blood is increased.

13. Acidosis was present in the cases examined, as determined by the carbon dioxid combining power of the blood plasma, the H ion concentration of the blood, and the carbon dioxid of the alveolar air.

The following references may also be consulted:

Addis: *Archives Int. Med.* **15**:413, 1915.

Abderhalden: *Ztschr. f. Biol.* **21**:483, 1900.

Asher and Grossenbacher: *Biochem. Ztschr.* **17**:78, 1909.

Austin and Pearce: *J. Exper. Med.* **20**:122, 1914.

Biedl and Kraus: *Ztschr. f. Immunitätsforsch.* **15**:447, 1912.

Hurwitz: *Bull. Johns Hopkins Hosp.* **26**:235, 1915.

TOXIN FORMATION BY A VARIETY OF *B. BOTULINUS*
WHEN CULTIVATED AEROBICALLY UNDER VARI-
OUS CONDITIONS: ITS POSSIBLE PRODUC-
TION IN THE ANIMAL BODY *

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Bacillus botulinus was first isolated by van Ermengem¹ who recovered it from meat that had produced an epidemic of botulism. He demonstrated that a soluble toxin secreted by the bacillus in the food was responsible for the condition and that the organism itself had no pathogenic power. That is to say, the bacillus was unable to produce the toxin under the conditions existing in the body.

The bacillus described by van Ermengem was a motile, sporulating anaerobe. This organism fermented dextrose, but did not coagulate milk. It required the presence of peptone in a neutral or slightly alkaline medium for toxin production. At temperatures above 30 C. toxin formation was inhibited. (This latter fact alone explained its lack of pathogenicity in animals having a temperature of 37 C.)

Although an obligatory anaerobe when in pure culture, van Ermengem and others showed that *B. botulinus* produced its toxin in the presence of oxygen when grown in symbiosis with certain aerobes.

Rabbits, cats, guinea-pigs, mice and monkeys are susceptible to the toxin. Chickens and frogs are not affected.

The symptoms produced are not those usually seen in a gastrointestinal intoxication. After an incubation period of from twenty-four to forty-eight hours there arise symptoms referable to the action of the toxin on the nervous system. In animals death is preceded by general motor paralysis and dyspnea, with secretion of mucus from the nose and mouth.

Postmortem, there is seen a general hyperemia of the organs with parenchymatous degeneration and minute hemorrhages. Amongst other changes, the muscles of the heart show signs of degeneration.

The work of van Ermengem has been confirmed in numerous instances. Recently there have been described in this country cases which vary somewhat from the original description.

*The latter part of this paper consists of preliminary notes not intended originally for publication. Further work along these lines has been postponed indefinitely, and for this reason it is thought best to publish what has been accomplished at the present time.

1. Kolle and Wassermann: Handbuch der path. Mikroorganismen, Ed. 2, 4:922.

Wilbur and Ophüls² reported an epidemic at Stanford University which apparently was caused by canned beans. That is to say, the toxin was produced in the absence of animal protein. Postmortem, they described a condition of thrombosis in the blood vessels at the base of the brain. In both of these points the epidemic varied from the original. No organism was isolated.

Later Dickson³ experimented with two strains of *B. botulinus*, one obtained from the New York Museum of Natural History, the other from Zinsser of Columbia. He concluded that "animal protein is not essential for the development of the toxin of botulism," that "an acid reaction of 3.2 per cent. to phenolphthalein does not prevent the formation of toxin," that "the toxin produces some disturbance of the circulatory system which leads to hyperemia and hemorrhages in the meninges and in the central nervous system, and to thrombosis in the arteries and veins of the meninges and of the central nervous system" and that "the lesions in the nerve cells are not due to a specific action of the toxin on the cell protoplasm, but they are secondary to disturbances of blood supply."

In another instance Nevin⁴ isolated from cottage cheese that had caused three deaths an organism closely resembling *B. botulinus* of van Ermengem. In this epidemic the clinical diagnosis was not made, and no organism capable of producing the symptoms was recovered postmortem.

The organism isolated from the cheese by Nevin was diagnosed as *B. botulinus*, but differed from this organism in the following particulars: It formed its toxin in a medium containing only the peptone of the meat, from which the medium was made, and it produced this toxin readily at 37 C.

These are very important variations from the organism of van Ermengem. Indeed, the production of toxin at 37 C. renders its nonpathogenicity a matter of doubt. Further, the fact that *B. botulinus* produces its toxin under aerobic conditions when cultivated with certain aerobes, and that according to Dickson³ a reaction of +3.2 does not entirely inhibit its production, and that animal protein is not essential, would indicate that toxin formation by *B. botulinus* might occur under conditions not generally thought possible.

EXPERIMENTAL

In the following experiments an attempt was made to study toxin production under unfavorable conditions such as might occur within and without the animal body in nature.

2. Wilbur and Ophüls: Archives Int. Med. 14:589, 1914.

3. Dickson: Botulism, An Experimental Study, J. A. M. A. 65:492, 1915.

4. Nevin, Mary: A Study of Cheese Causing Three Fatal Cases of Botulism. Read in abstract before the Conference of The American Public Health Association, Rochester, N. Y., Sept. 8, 1915.

The strains used by Dickson originally from Zinsser and the New York Museum of Natural History were found to have lost their toxin forming power as noted by Nevin. But the Nevin strain produced a powerful toxin and was used throughout the work.

The organism was found to differ somewhat from *B. botulinus* of van Ermengem in its behavior towards lactose. In mediums containing this sugar *B. botulinus* grows with difficulty, according to van Ermengem, who recommends dextrose as an enriching substance. The strain isolated by Nevin, on the contrary, grew very profusely in mediums containing from 1 to 2 per cent. lactose. In the hands of the writer it did not ferment this sugar with production of acidity or gas in spite of the fact that it possessed the power of acidifying and peptonizing milk. But according to Nevin it does possess this power.

In dextrose mediums it produced fermentation, as does *B. botulinus* of van Ermengem. The acidity of this reaction supposedly is not favorable to the toxin. Since growth without acidity occurred in the presence of lactose this substance was used instead of dextrose. Anaerobically, in sugar-free meat extract medium, the organism failed to grow.

One per cent. lactose agar of a neutral reaction was employed for the stock cultures and for testing the power of the organism to multiply under aerobic conditions. For toxin production it was cultivated in a broth adapted from that advocated by Rideal and Walker for testing disinfectants. This medium has the following ingredients:

	Gm. or c.c.
"Liebig's" extract of meat.....	20
Peptone (Witte's)	20
Salt	10
Distilled water	1,000

To this was added 20 gm. of lactose and the product was then made alkaline to the point of -0.5 . This medium will be referred to as L. R. W. broth.

Tests for Toxicity.—The toxicity of the Nevin organism was first tested against rabbits subcutaneously. In the preliminary experiment a very large dose was used. Two c.c. of a ten-day culture in L. R. W. broth grown anaerobically at about 30 C. in the dark were given by subcutaneous injection to a rabbit weighing 1,465 gm. Nineteen hours later the animal was found moribund, with all the muscles relaxed and saliva dribbling from the mouth. In another hour death occurred. The postmortem was performed immediately, and the following lesions were observed:

There was no gas in the tissues; serous exudate with some hemorrhage at the seat of inoculation; peritoneum and mesentery injected and organs, in general, hemorrhagic with the exception of the spleen, which appeared normal. The diaphragm and wall of the heart were likewise injected. Smears from the exudate, liver, spleen and heart's blood showed no organisms except for a few doubtful coli-like bacteria in the exudate. The organism was recovered in

pure culture by anaerobic methods from the heart's blood, liver and spleen. The culture from the heart's blood was retained and used in some of the experiments to be described, as it was believed that its toxin producing power might have been increased. It will be referred to as the H. strain.

The toxicity of the same strain when given per os was now tested. One c.c. of a four-day old culture grown as in the preceding experiment was placed on a little uncooked oatmeal, which completely absorbed the liquid. This preparation was given to a rabbit weighing 2,080 gm. The following morning the animal was observed to crawl instead of hopping in the usual fashion. No other symptom was noticed. On the second day the rabbit was unable either to hop or crawl, and died about fifty-four hours after eating the oatmeal. Postmortem the following points were observed:

There was marked injection subcutaneously, in mesentery, around the gut, on the stomach wall and in the diaphragm. The liver and spleen were congested and enlarged. The kidneys appeared normal. The bladder was full. Two lobes of the lungs were markedly congested. The heart was swollen and firm, and the vessels congested. There was no increase of fluid within the pericardium. Anaerobic cultures in L. R. W. broth from the heart, liver and spleen failed to show any growth.

One c.c. of the H. strain, made directly from the heart's blood of the first rabbit after three days' growth under similar anaerobic conditions, was next placed on some oats in a pan and given to a rabbit weighing 1,305 gm. The animal ate very little of the oats and since most of the culture trickled to the bottom of the pan only a very small portion of the broth could have been consumed. Yet on the morning following, the rabbit showed symptoms of weakness of the hind legs and lack of control of urine. In the afternoon of the same day the animal died, a little over twenty-four hours after ingestion of the poison. No postmortem was performed.

Finally, 0.1 c.c. of a five-day anaerobic culture of the original strain was placed in 1.0 c.c. of water, poured on a little oatmeal and given to a rabbit weighing 1,470 gm. The animal at first refused to eat this food, which was not consumed until the middle of the following day. No symptoms were apparent during the next twenty-four hours, but on the succeeding morning, about forty-five hours after the ingestion of the toxin, the rabbit appeared moribund, lying quietly on his side and dying soon.

The postmortem revealed marked injection of the blood vessels subcutaneously, around the gut, in the diaphragm, and on the heart wall. The spleen, liver and kidneys were markedly congested, but the lungs only moderately so. Slight hemorrhage was observed within the pericardium. Anaerobic and aerobic cultures were negative.

The importance of these experiments in which the toxin was given per os lay in the smallness of the lethal dose. For the toxin of *B. botulinus* of van Ermengem produces death under similar conditions only in doses of 5 to 10 c.c.

When tested against the cat the organism was not found to possess markedly toxic power, either per os or subcutaneously. One c.c. of a four-day anaerobic culture of the H. strain was given by stomach tube to a cat weighing 2,000 gm. The next day the animal's hind legs seemed a little stiff and in the afternoon it refused meat. The following morning a trembling in the tail was noticed, but in the afternoon the appetite returned, and from that time on no further symptoms were noticed.

To another cat was given a piece of meat in which had been injected 1 c.c. of a twelve-day anaerobic culture. This animal developed no symptoms.

A third cat was injected subcutaneously with 1 c.c. of a two-weeks-old culture of the same strain. On the following morning marked weakness in the hind legs was observed and the animal evidently preferred the dark. However, meat was not refused, and the symptoms gradually disappeared in the course of four days.

Another cat injected subcutaneously with 1 c.c. of a four-day anaerobic culture of the original strain failed to develop any symptoms during the first week, at the end of which period it was discarded.

The resistance of the cat to doses of 1.0 c.c. given subcutaneously differs from the reaction of the animal to the toxin produced by the strain of van Ermengem which caused death in quantities of from 0.1 to 1.0 c.c. But it should be noted that according to Nevin⁴ the toxin of the organism produced typical symptoms in kittens.

In regard to chickens and frogs, the organism of Nevin when fed per os acted according to the descriptions of *B. botulinus* of van Ermengem. In doses of 5 c.c. neither strain had any noticeable effect on two chickens fed with corn meal moistened with the cultures.

One frog was injected with 1.0 c.c. of the original strain, and another frog was placed in a jar containing 1.0 c.c. of the culture mixed with a little water. Neither developed any symptoms.

A third frog was placed in a jar containing 2 c.c. of the H. strain. It, likewise, failed to show any bad effects during a period of a week.

Finally⁵ the toxicity of the organism for horses when given per os was tested. For this purpose a four-day anaerobic culture of the H. strain in L. R. W. broth was used. Ten c.c. of this preparation were poured on some oats and given as feed to a young colt. Opportunity for close study of any symptoms was not available, but up to 5 a. m. of the second day after ingestion of the toxin, no symptoms were observed by the stable attendants. Three hours later, at 8 a. m., about forty-four hours after eating the oats, the animal was found dead. The postmortem was performed the same morning by Dr. Buckley and the following points noted:

Engorgement and inflammation of the jejunum and lungs; slight hemorrhages on the heart wall; engorgement of the lymph gland near the spleen and slight injection of the meninges. Transfers from the heart's blood, liver and spleen kept under anaerobic and aerobic conditions were sterile.

Experiments in Forage Poisoning.—The fatal result following the ingestion of the culture by the horse confirmed the possibility of the Nevin organism being the causative factor in forage poisoning and led to an attempt to reproduce this disease by treating forage with preparations cultivated under aerobic conditions similar to those found in nature. At the same time an effort was made to demonstrate the extent to which this organism might be cultivated in symbiosis with an aerobe in the presence of oxygen and still retain its toxin producing power.

Since the food supposed to be responsible for forage poisoning is frequently heavily seeded with yeasts, a variety of this species was chosen as symbiotic organism. It possessed the following characteristics:

Milk: Not changed.

Gelatin: Not liquefied.

Broth: Growth in form of sediment; no turbidity.

Dextrose: Acid and gas.

Lactose: No acid; no gas.

Saccharose: Acid and gas.

Pathogenicity: No effect on rabbits when injected subcutaneously in doses of 5 c.c., or when given per os.

5. The data in regard to the effect of cultures on horses has already been published by Dr. John S. Buckley of the Bureau of Animal Industry, in the Journal of American Veterinary Medical Association, March, 1917, New Series, Vol. 3, No. 7. His paper was first presented at the meeting of the A. V. M. A., Detroit, Mich., Aug. 21-25, 1916. For reasons apparent in the conclusions, this data is now reprinted. This part of the work was performed in order to demonstrate whether or not the organism may be the causative factor in the disease of horses commonly known as forage poisoning.

This yeast was grown on wort agar, and whenever transfers were made to preparations containing the Nevin organism a loop was used, since it had been previously determined that the latter organism grew irregularly when small quantities of the yeast were collected with a wire. The culture employed was that recovered from the heart's blood of the first rabbit, and which had been used in the case of the horse.

The cultures were kept under aerobic conditions on top of the incubator covered by a black cloth to protect them from the light. The temperature ranged from 25 to 32 C.

The mediums on which the mixed cultures of the Nevin organism and the yeast were grown consisted of ordinary 1 per cent. lactose agar slants and the L. R. W. broth already described. A trace of dextrose was probably present in both instances.

Transfers were first made from an anaerobic lactose agar preparation of the Nevin organism to two tubes of the L. R. W. broth. To one tube was added a heavy inoculation from a wort agar culture of the yeast.

After three days turbidity appeared in the preparation containing both bacillus and yeast, and a hanging drop showed the presence of motile bacilli. The yeast was present in the sediment, but only in very small numbers in the supernatant fluid. In the tube inoculated with the anaerobe alone no turbidity appeared during ten days, and no trace of the organism could be observed microscopically, indicating that no aerobic contamination existed in the anaerobic culture from which the aerobic preparation was made.

The mixed culture was now transferred to two lactose agar slants, and to one of them was added a loopful of the yeast.

After forty-eight hours a few colonies of the yeast were observed on the slant to which no additional yeast had been conveyed. Microscopically, yeast cells, but no bacilli, were seen. The other tube to which had been carried a heavy transfer of yeast showed an irregular growth in which appeared microscopically a few motile bacilli, without spores, mingled with the yeast cells.

This preparation was now transferred to two slants of the same medium over one of which, as in the previous case, a loopful of the yeast was smeared. After forty-eight hours the simple transfer showed microscopically many yeast cells and a few nonmotile bacilli without spores. The other tube to which the yeast had been conveyed showed the same picture except that motility was observed in the bacilli.

The latter preparation was transferred to a fresh tube of lactose agar with the addition of yeast as in the previous cases. No microscopic observations were made. After three days this culture was again conveyed to two slants of lactose agar, and to one of these yeast was added. At the end of forty-eight hours both these tubes showed irregular, heaped-up growths. Microscopically, there were seen numerous bacilli along with a few spores in addition to the yeast cells.

This process was repeated, and in forty-eight hours both the simple transfer and the culture with additional yeast showed microscopically equally numerous motile bacilli mixed with the yeast. Therefore, the further addition of yeast was not considered necessary, and the simple transfer was selected and conveyed by means of a loop to a fresh lactose agar slant.

In this preparation after three days the motile bacilli were found to be present in small numbers. From this tube another transfer was made, and again in three days the same picture was seen, except that some spores were noted as well.

This culture was transferred to a final lactose agar slant and then the medium was changed in order that the organism might be given an opportunity to produce its toxin in a liquid. After two days' cultivation the final lactose

agar preparation was carried with a loop along with a fresh supply of yeast to L. R. W. broth. Then after four days, and again after three days, transfers were made, with addition of yeast, from L. R. W. broth culture to L. R. W. broth.

In this latter preparation turbidity and sedimentation appeared in forty-eight hours. On the third day this increased, and microscopically in the supernatant fluid were seen motile bacilli with subterminal spores. In the sediment were yeast cells.

Thirty-two days had now elapsed since the first aerobic transfer and during this period the bacillus had been successfully cultivated for seventeen days on lactose agar slants by means of eight transfers.

The toxicity of the last broth culture of the Nevin organism and the yeast was next tested:

One c.c. of this culture was given by stomach tube to a rabbit weighing 1,760 gm.; 1 c.c. was injected into a piece of meat and given to a cat to eat.

No symptoms were noticed in the cat during a period of a week after ingestion of the food, but the rabbit began to show slight sluggishness after three days, and on the succeeding day was found dead in his cage.

The postmortem showed the usual findings somewhat intensified and there was also observed a marked congestion of both lungs, with the exception of part of one lobe, and a hemorrhagic pericarditis with blood clots. The surface of the kidney presented a curious pitted appearance. Smears and anaerobic and aerobic cultures from the heart's blood, liver and spleen were negative.

In the meantime the aerobic mixed culture was carried on in L. R. W. broth as formerly. That is to say, a fresh transfer with the addition of the yeast was made every three or four days. After three such transfers, at the end of a further period of twelve days, 1 c.c. of a three-days' culture was given by stomach tube to a rabbit weighing 2,180 gm. The next morning the animal was found dead. The postmortem was performed on the following day and showed a marked hemorrhagic congestion of the lungs and bloody fluid in the pericardium, with injection of the blood vessels of the heart wall and duodenum. Postmortem decomposition had set in and masked the findings.

At the end of another forty-eight hours 1 c.c. of the next transfer was dropped on a little oatmeal and given to a rabbit weighing 2,265 gm. The oatmeal completely absorbed the fluid and was entirely consumed by the following morning. Symptoms of weakness developed on the fourth day and the animal ceased to eat, although his jaws were observed to move as if chewing the food. After another period of two days this attempt also ceased, and during the next week the food placed in the rabbit's cage remained untouched. No symptoms other than those of weakness were observed. Then improvement set in and the animal was discarded after another week had elapsed. At this time he was able to eat and seemed apparently normal.

The next transfer was used to test the toxicity of the preparation for donkeys: 0.2 c.c. of the culture when three days old was placed in about 10 c.c. of sterile saline solution and given to a donkey by pouring on a little bran. The bran was consumed within two hours after being treated with the culture. As a control, 1 c.c. was placed on some uncooked oatmeal and given to a rabbit weighing 1,520 gm.

The rabbit developed no symptoms till the end of the second day, when a retraction of the neck was noted. On the following morning he was found dead. Postmortem, the animal showed the usual general injection of the blood vessels, and as in the first two rabbits, the lungs were congested. Hemorrhage had occurred in the pericardium. The kidney and liver were congested and the spleen was enlarged and of a pulpy consistency. Neither the Nevin organism nor the yeast could be recovered by anaerobic or aerobic methods.

The donkey became sick at the end of four days after the feeding. At this time he was seen by the caretaker of the stable to be lying down. The writer was not able to see the animal until another forty hours had elapsed, six days after ingestion of the culture. At this time the donkey was prostrate, breathing heavily, with dilated nostrils, from which a mucous fluid was dribbling. The animal was too weak to rise or walk unaided. When raised, he took a few steps supported by several men. He was then pushed back in the stall, where, after standing for ten or fifteen minutes, he fell. No symptoms indicating paralysis could be observed. On the following morning the donkey was dead. Opportunity for a postmortem did not occur before the next day, when decomposition completely masked any lesions that might have been present. No cultures were taken. The temperature chart for the first four days follows:

TEMPERATURE, DONKEY 1

Date	A. M.	Noon	P. M.
Feb. 15 '16 p. m.	Culture ingested.		98.2
Feb. 16	97.2	97.0	97.6
Feb. 17	97.2	96.4	98.6
Feb. 18	97.2	96.6	99.0
Feb. 19	96.0	97.8	96.8 marked ill-
Feb. 20			ness
Feb. 21			
Feb. 22	Death.		

In the meantime the mixed culture of *B. botulinus* and the yeast had been carried on in the usual manner by transferring every third day to L. R. W. broth, with the addition of yeast at each transfer. After two such transfers 1.0 c.c. was given on oatmeal to a rabbit weighing 1,460 gm. as a control, and 0.5 c.c. was given on bran to a second donkey.

The rabbit developed a slight weakness in the hind legs on the following day and was found dead the next morning, less than forty-eight hours after eating the food. The postmortem was performed at once, but decomposition had already set in. However, injection of the blood vessels in the subcutaneous region, in the diaphragm and around the wall of the duodenum could be made out. The lungs showed areas of congestion. Aerobic and anaerobic cultures from the heart's blood were negative.

The donkey on the second morning after eating the infected bran, that is to say, after a lapse of about forty-two hours, was observed to paw the earth and tremble in a manner to indicate the possible existence of some intestinal colic. No other symptoms were manifest. On the evening of the same day he seemed sluggish, but presented no definite signs of illness. However, on the morning of the third day, about sixty-six hours after eating the bran, he was found with the tongue completely paralyzed, protruding about 3 inches or more from the mouth. Food and drink were refused. The pulse was about 30 and somewhat weak. The temperature was 99. The sluggishness was more marked than on the preceding evening, but there were no signs of paralysis other than those evident in the tongue. At 2 p. m. of the same day the animal was noticed by the watchman, standing in his stall, the condition apparently unchanged. At 4 p. m. he was seen by the writer. At this time the donkey was lying down, too weak to rise without aid. When forcibly lifted, he was unable to stand alone, and when put back on the ground lay quietly, with apparent consciousness of his surroundings. The tongue still protruded, but no other signs of paralysis could be noted. About midnight the donkey died, in the neighborhood of three days and eight hours after eating the bran, and fifteen hours after the first serious symptom, paralysis of the tongue, was observed. The temperature chart, taken by the stable attendant, follows:

TEMPERATURE, DONKEY 2

Date	A. M.	Noon	P. M.
Feb. 21 '16	p. m., culture ingested.		99.2
Feb. 22	98.0		99.0
Feb. 23	98.0		98.0
Feb. 24	99.0	97.8	97.0 Death 12 M.

The postmortem was performed by Dr. Buckley about ten hours after death had occurred, before any signs of decomposition had set in. The following points were noted:

Subcutaneous vessels not markedly injected.

Stomach: Vessels in outer wall injected. Inner wall shows areas of shallow erosions. Mucous membrane is quite pale and coated with mucus.

Duodenum: Outer wall shows areas of hemorrhage in patches. On inner wall are punctate and larger areas of hemorrhage.

Jejunum: Outer wall like that of duodenum, except that areas of punctate hemorrhage are present in addition to the larger patches. The inner wall shows a condition intermediate between the duodenum and ileum.

Ileum: Outer wall like that of jejunum, but lesions are more marked. On inner wall is seen a condition of diffuse hemorrhagic enteritis.

Cecum: Outer wall normal. Inner wall shows numerous punctate hemorrhages.

Colon: First part reddened on outside. Stained on inside. Second and third parts normal and full of feces.

Mesentery: Larger vessels are injected.

Spleen normal.

Liver slightly congested.

Kidney markedly congested.

Diaphragm, no marked injection.

Lungs markedly congested.

Heart wall, no points of hemorrhage.

Pericardium normal.

Bladder full but not distended.

Cerebrospinal fluid, normal in quantity at junction of head with body.

Cultures were made from the heart's blood, liver and spleen in L. R. W. broth, on plain agar and on wort agar. The L. R. W. broth cultures were placed under anaerobic conditions. The others were kept aerobically. All were kept at a temperature of between 25 and 30 C. On none did any growth develop.

These experiments indicate that the organism, although in pure culture an obligatory anaerobe, may be cultivated in mixed culture with a yeast under aerobic conditions such as exist on an aerobic slant agar preparation.

Effect of Light on Toxin Production.—The effect of light on the production of toxin was next studied. The medium employed consisted of 2 per cent. lactose R. W. broth of reactions varying from neutral to about +2. Traces of dextrose were present. About 10 or 15 c.c. were kept in each tube. A tube of this medium was inoculated from a dextrose agar preparation of the same strain used in the previous experiments, and with the yeast from a twenty-four-hour wort agar culture. Other tubes were inoculated with simple transfers of the two organisms. All the preparations were kept on the desk in front of a window at temperatures ranging from 20 to 30 C. The window faced the North, and the sunlight did not fall on the cultures.

In the tube containing the Nevin organism alone no growth developed. In the tube to which the yeast had been transferred there occurred a sediment without turbidity. Microscopically only yeast cells could be demonstrated. It may, therefore, be inferred that the cultures used contained no aerobic contamination capable of growing in broth.

In the tube containing both anaerobe and yeast there developed in forty-eight hours the usual turbidity, sediment, and foul odor. The hanging drop revealed the presence of motile bacilli with subterminal spores, and yeast cells.

After the culture was five days old 1 c.c. was dropped on some uncooked oatmeal and given to a rabbit weighing 1,620 gm. This was consumed by the following morning. Twenty-four hours later the rabbit ceased to eat. After another interval of forty-eight hours the animal was found dead. From the condition of the body death probably occurred between forty-eight and seventy-two hours after eating the oatmeal. Postmortem there was observed the decomposition that was to be expected and the usual injection of the blood vessels and engorgement of the liver. The lungs were markedly hemorrhagic, only a few areas being unaffected.

The culture was kept alive by transferring every five or ten days to fresh L. R. W. broth with the addition of yeast. The tubes were kept on the desk in the light under aerobic conditions. After being thus grown for twenty-three days a five-day culture was given in dose of 1 c.c. by stomach tube to a rabbit weighing 1,785 gm. No symptoms developed until the afternoon of the fourth day after the feeding. Then the animal was observed to make continual efforts to swallow without eating. The following morning this persisted and in addition the neck was retracted. There was no paralysis of the limbs. At 3:30 p. m. the rabbit was found dead and stiff, with neck retracted.

The postmortem showed a tumor above the umbilicus connecting with the region of the spine and a hemorrhagic fibrinous exudate beneath the skin. The peritoneum, mesentery, diaphragm and heart wall were injected. The heart wall was congested. The lungs were normal, except for one small area of hemorrhage. The liver was congested. The spleen was normal. Cultures made anaerobically and aerobically from the heart's blood were negative.

After being grown in the light on the desk for two and one-half months, with transfers every five or ten days, 5 c.c. of a fourteen-day culture were given by stomach tube to a rabbit weighing 1,890 gm. No symptoms were observed the following day. At 4 p. m. the rabbit ate part of a carrot. The next morning, less than forty-eight hours after ingestion of the culture, it was found dead, with eyes open, lying on the side, without any signs of a struggle. The carrot given the previous afternoon was half consumed. Postmortem, there was seen the usual injection, and in addition there was one large area of hemorrhage on the upper gut. The lungs were engorged. The heart swollen, firm, congested. The vessels of the diaphragm were markedly injected. The spleen and kidney were about normal.

These experiments indicate that exposure to daylight for two and one-half months does not inhibit the toxin production to any marked degree.

Effect of Heat on the Toxin.—The effect of heat on the toxin and on the toxin-forming power of the bacillus was now taken up.

A five-day aerobic mixed culture in L. R. W. broth grown at temperatures under 26 C. was selected. As a control, 1 c.c. of this culture was given by stomach tube to a rabbit weighing 1,785 gm. Then the preparation was heated to from 65 to 70 C. for twenty minutes, and 2 c.c. of this were injected subcutaneously into a rabbit weighing 2,460 gm. The control developed symptoms four days later and died on the following day. The postmortem showed the usual findings. The other rabbit failed to develop any symptoms during eight days following the inoculation.

This experiment was repeated, with the variation that the heated culture was given per os instead of subcutaneously, and the period of observation lengthened in order to determine the ability of the spores to develop in the rabbit's intestines. Ten c.c. of a thirteen-day mixed culture grown aerobically in L. R. W. broth at a temperature of 30 C. in the incubator and heated to from 65 to 70 C. for twenty minutes were given by stomach tube to a rabbit weighing 2,400 gm. At the end of six weeks no symptoms had developed and the rabbit weighed 2,335 gm.

These experiments confirmed those of many other workers in regard to the destruction of the toxin by moderate amounts of heat, and indicated that the spores of the organism were not pathogenic when given subcutaneously or per os.

Regaining Toxicity After Heating.—To demonstrate the possibility of a heated culture regaining its toxicity, the following experiments were undertaken.

A five-day mixed culture grown aerobically on the desk at temperatures below 25 C. was heated to from 65 to 70 C. for twenty minutes. As a control, 2 c.c. of this preparation were placed on raw oatmeal and given to a rabbit weighing 1,980 gm. The food was not entirely eaten till three days had elapsed, but since no symptoms developed in the ensuing four days, and since other experiments had shown that heated cultures were not toxic, it may be concluded that in this case as well the heat applied had rendered the toxin harmless.

Since in the original heated culture the yeast had been killed, the remaining spores of the anaerobe could not be expected to develop aerobically and produce toxin without the addition of a fresh supply of yeast. Accordingly, immediately after cooling, a fresh transfer of yeast was made to the culture and the preparation placed on the desk. After a week had elapsed, during which time the temperature ranged under 26 C., 1 c.c. of this preparation was placed on oatmeal and given to the same rabbit, whose weight was now 1,970 gm. The food was consumed during the next forty-eight hours, but no marked symptoms developed during the six days following the giving of the culture. To determine its toxicity finally, 2 c.c. of this same preparation, thirteen days having passed since the heating, were injected subcutaneously into the rabbit at 3 p. m. The following morning the animal was found dead, lying stretched out in the cage with no evidence of convulsions having occurred. Death had ensued in from twelve to eighteen hours.

Postmortem there was observed a serofibrinous exudate beneath the skin, without noticeable hemorrhage. There was some injection of the peritoneum and mesentery. The heart was swollen, but not otherwise abnormal. The lungs showed no congestion. The diaphragm was thickened, and the vessels injected. The liver was congested, the spleen markedly enlarged and congested, the kidneys congested, the bladder full and the vessels injected. Cultures from the heart's blood were negative.

On account of the failure of the control rabbit to eat the oatmeal immediately on being offered, and on account of too short a time being allowed for observation, it is not possible to draw any very definite conclusions from this preliminary experiment. However, it would indicate that contaminated food heated sufficiently to destroy the toxin but not to kill the spores may again become toxic.

Effect of Drying on Toxicity.—To test the effect of drying on the toxin-producing power of the bacillus a small piece of filter paper was saturated with a seven-day mixed culture made in L. R. W. broth. This was placed in a sterile test tube and allowed to dry out on the desk for twenty-two days. Then it was transferred to a tube of L. R. W. broth along with additional yeast. This preparation was placed in the incubator at 30 C. After four days, turbidity and odor were noted.

When the culture was seven days old 2 c.c. were given by stomach tube to a rabbit weighing 1,505 gm. No symptoms appeared the following day. On the second day no observations could be made. On the third day, seventy-two hours after ingestion, the animal was found dead. No postmortem could be performed. Apparently drying for twenty-two days fails to destroy the toxin-producing power of the organism.

Toxin Production at Different Temperatures and Reactions.—According to Dickson, *B. botulinus* may produce its toxin in medium of reaction of over +3,

and according to Nevin the organism isolated by her produces toxin at a temperature of 37 C. To test these observations broth was made according to the following formula:

	Gm. or C.c.
"Liebig's" extract	5
Armour's peptone	10
Salt	5
Water	1,000

Different lots were titrated to 0, +1, +2, +3 and +4 cold, and 10 c.c. measured into tubes. After autoclaving, a tube of each titration was inoculated from a mixed culture of the Nevin organism and yeast grown four days in L. R. W. broth at 30 C. and an additional transfer of yeast was added. The preparations were placed in the incubator at 38 C. In twenty-four hours faint turbidity without odor appeared in the tube of reaction 0. More marked turbidity with odor appeared in tubes of reaction +1 and +2, and no turbidity in tubes of reaction +3 and +4. Since the yeast grows poorly in neutral or alkaline medium and since in pure culture the Nevin organism will not grow aerobically, it was to be expected that a moderate acidity would give the best symbiotic growth.

In seventy-two hours turbidity and some odor was observed in the +3 tube. On examination in the hanging drop, tubes of reactions 0, +1 and +2 showed large motile bacilli, extracellular spores and yeast cells. Tube +3 showed fewer, larger bacilli with intracellular spores and yeast cells, and tube +4 only yeast cells without bacilli.

When the cultures were seven days old a transfer was made from the +3 preparation to a similar tube of +3 broth and additional yeast added. This was likewise placed in the incubator at 38 C. In it there developed turbidity and odor, and when five days old 1 c.c. was taken and given by stomach tube to a rabbit of 1,730 gm. weight. At the same time a further transfer to +3 broth tube was made with addition of yeast. During the next six days no positive symptoms developed in the rabbit, so at the end of this period 5 c.c. of the six-day old culture, made when the first dose was given the rabbit and grown at 38 C., were given to the same rabbit by means of a stomach tube. The following day the animal was sluggish, and in forty-eight hours it ceased to eat. In seventy-two hours, on the morning of the third day after ingestion of the last dose, it appeared very apathetic. The muscles were relaxed and it did not eat. No paralysis was observed. At 3 p. m. the same day it was very weak, the muscles of the abdomen greatly relaxed, and the breathing labored. There was no paralysis. On being placed on the floor it hopped quite energetically, but on being returned to the cage died in convulsions as if from embolus.

Postmortem, the injection in the mesentery around the gut was very marked. The liver and spleen were engorged. The diaphragm was injected. The lungs appeared normal except for one small dark area in one lobe that resembled an infarct. The heart was distended and engorged. Transfers from the heart's blood were negative.

This experiment confirms the observations of Dickson and Nevin in regard to reaction and temperature. It would indicate that in the absence of sugar a weakened toxin is formed in meat extract broth of reaction of +3 at 38 C.

These points do not coincide with the observations of van Ermengem and others in regard to the original strain of *B. botulinus* and indicate that while the organism isolated by Nevin may be a variety of *B. botulinus*, its requirements for toxin production make it theoretically a much more dangerous organism. For since it can produce

toxin at body temperature under aerobic conditions in a medium of +3, it is possible that it might grow in the human intestine, or in the throat in symbiosis with an appropriate aerobe.

That it fails to produce toxin in the intestines of the rabbit has been shown in an experiment already recorded. This may be due to some inhibiting effect of intestinal organisms such as *B. coli* or *Bact. welchii*. In the throat its growth would to a great extent depend on its power to multiply in symbiosis with streptococci, *Micrococcus aureus* and other bacteria commonly found in infections, and to its ability to withstand the inhibiting influences which the body tissues possess.

Opportunity to solve all these questions was not available. To test the ability of the Nevin organism to produce toxin in the presence of *B. coli*, *Bact. welchii*, and *M. aureus*, the following experiments were undertaken.

Toxicity in Presence of Other Organisms.—In the first series sterile milk was used as a medium. About 10 c.c. were placed in each tube. One was inoculated from an eight-day broth culture of *B. coli* and with a mixed culture of the Nevin organism and yeast grown eight days aerobically at 30 C. in L. R. W. broth. To another tube was transferred the Nevin organism and yeast culture, along with a transfer from a three-day wort agar culture of the yeast. Two other tubes were inoculated with single transfers from the *B. coli* and the yeast culture as controls. All were kept aerobically at 30 C.

In the course of a week the yeast caused no change in the milk. In twenty-four hours *B. coli* produced acidity with slight reduction. In seventy-two hours no coagulation occurred. In thirteen days there was coagulation, with little whey formation, together with some reduction of the litmus and a sweetish odor.

In twenty-four hours the yeast and Nevin organism caused no change. In seventy-two hours there was about 90 per cent. peptonization. After thirteen days there appeared a heavy scum. The odor was very foul.

The yeast, Nevin organism and *B. coli* culture caused a reduction in the litmus in twenty-four hours. In seventy-two hours it produced coagulation with little whey formation. In thirteen days the milk was 50 per cent. peptonized. The odor was sweetish. Here the peptonization would indicate the growth of the Nevin organism, but the lack of foul odor would indicate the opposite.

Hanging drops made from the whey of the yeast and Nevin organism preparation showed bacilli of the general type of *B. botulinus* with subterminal spores. There was no motility. The yeast was present. No explanation of the scum was found unless it was formed by the yeast.

Hanging drops from the whey of the *B. coli*, Nevin organism and yeast culture showed many large and small nonmotile bacteria and many yeast cells. There were no spores and no bacilli of the general morphology of *B. botulinus*. Apparently *B. coli* had inhibited the growth of the Nevin organism. As a final test the two cultures, now evaporated down to about 7 c.c., were given to two small rabbits by stomach tube. The yeast and Nevin organism was given to a rabbit weighing 910 gm. The *B. coli*, Nevin organism and yeast preparation was given to one of 955 gm. weight. The cultures at the time were fourteen days old.

The following morning, twenty-four hours after ingestion, no symptoms were observed in either rabbit. At midday both were well. At 2 p. m. of the same day the rabbit treated with the yeast and Nevin organism preparation was

found dead. The postmortem revealed slight subcutaneous injection. Around the gut this was more marked; the liver was engorged; the diaphragm injected; the upper lobes of the lung showed a hemorrhagic condition; the heart was still beating when examined; it was apparently normal. Cultures made from the heart blood were sterile.

At 4:30 p. m. of the same day the remaining rabbit was lively. At 9 a. m. of the following morning it was found dead and stiff, and had apparently been dead some time. Less than forty-eight hours had elapsed since the ingestion of the culture. Postmortem decomposition had set in. The animal was very rigid. Injection of subcutaneous and mesenteric vessels was present; the liver was engorged; the spleen normal; the heart normal; the upper lobes of the lungs were markedly hemorrhagic.

It is therefore evident, in spite of the Nevin organism not being demonstrable microscopically in the mixed culture, that *B. coli* has not the power of suppressing the growth of the Nevin organism in milk.

The experiment in regard to *Bact. welchii* was not completed by animal testing on account of lack of time. In the preliminary work *Bact. welchii* was first grown aerobically with the yeast in broth, and this was used as a stock culture. Tubes of plain broth of reaction +1, of neutral L. R. W. broth, and of 2 per cent. dextrose broth were inoculated from a twenty-four-hour culture of *Bact. welchii* and yeast, and from an eight-day culture of the Nevin organism and yeast in neutral L. R. W. broth. One set was placed at 30 C., one at 39 C. After twenty-four hours, motile bacilli could be demonstrated in the neutral, L. R. W. and plain broth cultures kept at 30 and 39 C. But in the 2 per cent. dextrose cultures, both kept at 30 and 39 C., no motile bacilli of the morphology of *B. botulinus* could be demonstrated, but only nonmotile fat bacteria of the type of *Bact. welchii*. This would indicate that *Bact. welchii* cannot inhibit the Nevin organism in the presence of lactose alone, or in the absence of sugar, but that it has some inhibitory power in the presence of dextrose. However, the lack of animal tests renders this inconclusive. Yet it is possible that the presence of both dextrose and *Bact. welchii* in the rabbit's intestine is a cause for the nonpathogenicity of the Nevin organism under these conditions.

In regard to the growth of the Nevin organism in symbiosis with *M. aureus*, the following experiment was performed.

A tube of plain extract broth of acidity +1 was inoculated from pure agar cultures of *M. aureus* and the Nevin organism and placed at 38-39 C. The *M. aureus* strain selected was one which had produced typical lesions in the rabbit. In twenty-four hours turbidity appeared and in the hanging drop could be seen motile bacilli with subterminal spores. In seven days the hanging drop showed cocci, extracellular spores and nonmotile bacilli of the general morphology of the Nevin organism. Five c.c. of this culture were given by stomach tube to a rabbit weighing 2,419 gm. On the following day no symptoms developed. Two days later, three days after ingestion of the culture, the rabbit was found stiff and decomposed. It had evidently died between twenty-four and forty-eight hours after ingestion. In spite of the decomposition there could be made out marked injection of the vessels in the subcutaneous tissue, mesentery and diaphragm; the liver was engorged; the spleen was somewhat enlarged; the kidneys pitted; the upper lobes of the lungs were markedly engorged; the lower lobes were not affected. No cultures were taken

SUMMARY

The organism isolated by Nevin from cottage cheese that had caused an epidemic diagnosed postmortem as botulism is a distinct variety of the *B. botulinus* of van Ermengem.

It differs from this organism in the following particulars:

It is more toxic for rabbits.

It is less toxic for cats.

It grows and produces toxin at 37 C. and in sugar-free media of acidity of +3.

In the rabbit it produces symptoms and lesions not identical with those described by van Ermengem.

Although stock cultures obtained as *B. botulinus* were found non-toxic, the organism of Nevin produced toxin after resisting the effect of light for two and one-half months and of drying on paper for twenty-two days.

In symbiosis with a yeast, it can be cultivated aerobically on agar slants. Grown with *B. coli* and a yeast in milk, it produces death when ingested by a rabbit. Grown with *M. aureus* in extract broth at 38-39 C., under aerobic conditions it likewise produced death when ingested by a rabbit.

In numerous instances the toxin produced death in the rabbit without any preliminary symptoms being observed. In one case in which the toxin was produced in +3 broth, death apparently was associated with infarct of the lung and embolus.

The nonpathogenicity of this strain is not definitely proved. In the intestines of the rabbit the organism apparently fails to grow, and injected subcutaneously the spores produce no symptoms. Yet the fact that it grows at body temperature in the presence of *M. aureus* renders it possible that in mixed infection in the throat or protected from the influence of the body tissues in some cavity of the teeth it may produce its toxin.

In the writer's experience few symptoms are to be observed in the rabbit when the toxin given is formed under aerobic conditions. Under these circumstances no definite paralysis of the limbs was observed, although the organism produced this symptom when grown anaerobically.

The postmortem findings of Ophüls and Dickson indicate that certain strains of *B. botulinus* may produce thrombosis and hemorrhage in the meninges and central nervous system.

These facts would seem to indicate that the toxin produced by the Nevin Strain might cause sudden death by embolus or hemorrhage in the brain, accompanied by but few preliminary symptoms of a minor character.

The culture is capable of killing donkeys when given on feed in doses as low as 0.2 c.c.

What is known of the etiology, symptomatology, and pathology of forage poisoning indicates that the disease may be caused by a toxin similar to that produced by *B. botulinus*.

No definite conclusions can be drawn from the few experiments performed, but in view of the facts mentioned it seems probable that some cases of forage poisoning may be due to certain strains of *Bacillus botulinus*.⁶

Finally, it should be observed that this organism presents manifold possibilities for use as a poison both for horses and men. The toxin of the variety of *B. botulinus* employed certainly possesses the power of killing horses in very minute doses when given in the feed.

In regard to the toxicity of the organism for man, it would seem at first glance that the symptoms produced would be those of botulism. For the organism was isolated by Nevin from cheese that had produced numerous cases of a disease diagnosed postmortem as botulism, and the symptoms of this disease are well known and should be capable of diagnosis.

But there always remains the possibility of the organism growing in the body and producing its toxin slowly and under altered conditions, thereby causing a different syndrome from that seen when the toxin is ingested.

It is noteworthy that the most marked, constant lesion produced in the rabbit, horse and donkey was a congestion of the lungs, *when the culture was ingested by the animal*. In the first preliminary experiment on the rabbit, and in one other in which the culture was injected subcutaneously, this lesion was not noticed, nor is it apparent in Nevin's⁴ work in which injections were used throughout. Apparently then, the organism is capable of producing various lesions. Certainly the pathologic findings in rabbits which had ingested cultures grown in symbiosis with a yeast under aerobic conditions would not lead one to make the diagnosis of botulism if these lesions had been found in man. Again, the dosage would probably affect the symptoms. In large doses sudden death might be expected.

If placed in the water supply the organism might find conditions favorable for the production of a small amount of toxin, and since disinfectants have little effect on spore bearers, it is probable that treatment of such water by the hypochlorites would fail to kill the organism.

6. Since this statement was written the work of L. H. Pammel (Forage Poisoning Due to *Bacillus Botulinus*, Am. J. Vet. M. 13: No. 3, March, 1918) has strengthened the supposition.

THE MECHANISM OF THE PROTECTIVE ACTION OF CARBOHYDRATE DIET IN PHOSPHORUS AND CHLOROFORM POISONING *

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CHICAGO

In a series of experiments reported elsewhere¹ it was shown that the esterase content of the livers of dogs poisoned with phosphorus or with chloroform was not materially less than that of the livers of normal dogs, and that the feeding of liberal amounts of sugar causes an increase in the amount of this ferment in both normal and phosphorus poisoned animals. In another series of experiments,² using the same extracts as in those just mentioned, it was found that phosphorus poisoning causes an appreciable reduction in the ereptic power of the liver, that the feeding of sugar does not increase the ereptase content of the livers of normal dogs, but that it does prevent the diminution of this ferment when fed to animals which have been poisoned with phosphorus. These findings have led to the formulation of certain ideas as to the mechanism of phosphorus and chloroform poisoning, and of the detoxicating, antitoxic or sparing action of carbohydrate diet in poisoning with these substances. These conceptions are presented in this article.

The changes in the liver in phosphorus and chloroform poisoning, in acute yellow atrophy and in eclampsia, have much in common. In phosphorus poisoning the liver is large and fatty, the fatty change beginning in the peripheral part of the hepatic lobule, actual necrosis of the liver cells occurring *relatively* late. In acute yellow atrophy, the pathologic process begins in the central zone of the lobule as a fatty degeneration, proceeds rather rapidly to necrosis, and may ultimately involve the entire lobule. In chloroform poisoning the lesion also starts centrally as a fatty degeneration followed by early necrosis. In eclampsia, the fatty degeneration and early necrosis begin in the periphery of the lobule. All four of these conditions, therefore, have in common fatty degeneration and necrosis of the liver cells, the differences being chiefly in the location of the lesion in the lobule, the amount of visible fat present and the rate at which necrosis occurs.

*From the Laboratory of Pathology, Northwestern University Medical School.

1. Simonds, J. P.: J. Exper. M. 28:663, 1918.
2. Simonds, J. P.: J. Exper M 28:673, 1918

Of the four conditions mentioned, phosphorus poisoning shows the largest amount of visible fat. The intracellular droplets are relatively large so that the liver has the microscopic appearance of the so-called fatty infiltration. The work of Taylor,³ Rosenfeld⁴ and others has indicated that in phosphorus poisoning there occurs a transportation of fat to the liver from the fat depots of the body. But an additional change also takes place in the intracellular lipoids. Taylor³ found that if the fat was extracted from livers and the residue digested with pepsin and trypsin, a greater amount of fat could be extracted from the digests of normal than of phosphorus poisoned livers; that is, practically all the fat in the phosphorus poisoned livers was in a free state. This indicates that a considerable part of the fat in the liver exists normally in an invisible, unextractable combination which is broken up by phosphorus poisoning. In other words, in this pathologic condition there is both fatty infiltration and fatty degeneration. In chloroform poisoning and in acute yellow atrophy the changes in the liver are more of the nature of a fatty degeneration without so much infiltration with transported fat. The cells which are affected undergo a rather rapid necrosis. Rosenfeld⁴ observed that fat may become visible as fine droplets in dead or dying cells in the process of autolysis. For the taking up and storage of fat transported to the cells a certain amount of vital activity, as indicated by the presence of the nucleus, is essential (Dietrich⁵). In phosphorus poisoning the nucleus does not disappear so early and the cell retains its vitality for a sufficient time to permit the synthesis of fat from transported materials, and its accumulation within the cells in large droplets. Oppel⁶ even considers that the appearance of fat in the liver cells in phosphorus poisoning is not due to degeneration but to a stimulation of the cells to an increased endogenous formation of fat from exogenous materials.

A further important change in the cells of the liver in phosphorus and chloroform poisoning is the rapid disappearance of glycogen. The glycogen of the cells of the body may, as pointed out by Gierke,⁷ either form a more or less integral part of the cytoplasm, as in epithelium and cartilage, cells at some distance from the blood supply, and its amount is not readily affected by extracellular influences; or the glycogen may be the result of a process of storage, as in the cells of the liver and skeletal muscles. The quantity of storage glycogen is

3. Taylor, A. E.: *J. M. Research* 9:59, 1903.

4. Rosenfeld, G.: *Berl. klin. Wchnschr.* 41:587 and 617, 1904.

5. Dietrich, A.: *Arb. a. d. path. Inst. Tübingen* 5: No. 1, 1904.

6. Oppel, A.: *Arch. Entwicklungsmech.* 30: Part 1, 304, 1910.

7. Gierke, E.: *Ergebn. d. spez. path. Morph. u. Physiol. d. Sinnesorg.* (Lubarsch and Oestertag) 2: Part 2, 871, 1907.

easily altered by external factors, either increasing or decreasing, according to the nature of the influence at work. It may entirely disappear from the liver in starvation, in infections and after various types of poisonings. Doyon⁸ found decrease of glycogen of the liver after poisoning with abrin, a condition which Flexner⁹ showed was associated with necrotic changes in the liver. Andrea¹⁰ observed a similar reduction after injections of hemolytic serums which, as Pearce¹¹ and Karsner and Aub¹² have shown, are followed by localized necroses in the liver. Saikowski,¹³ Rosenbaum,¹⁴ Athanasiu,¹⁵ Rettig,¹⁶ and others have observed a rapid and complete disappearance of glycogen from the liver in phosphorus poisoning. Rettig also found that the liver lost its stored glycogen in chloroform poisoning.

Reports in the literature of studies of the enzymes in the conditions under discussion are not numerous. Whipple,¹⁷ Jobling, Eggstein and Peterson,¹⁸ Quinan,¹⁹ Sagal²⁰ and Simonds¹ have observed an increase in the serum esterase in phosphorus poisoning. Whipple,¹⁷ Quinan¹⁹ and Simonds¹ noted a similar increase in chloroform poisoning. Sagal²⁰ and Whipple¹⁷ record cases of puerperal eclampsia in which the serum esterase was augmented. According to Whipple,¹⁷ increase of the esterase of the serum indicates a destructive lesion of the liver.

The results of studies of the esterase content of the liver itself in these pathologic processes are strikingly conflicting. Jobling, Eggstein and Peterson¹⁸ and Quinan¹⁹ report a reduction of the esterase power of the liver in phosphorus poisoning. Winternitz and Meloy²¹ say that when microscopic fat is present in the liver its esterase content is reduced. Loevenhart,²² Ducchieschi and Almagia,²³ Saxl²⁴ and Simonds¹ found little or no change in the ester splitting activity of the livers of animals poisoned with phosphorus.

8. Doyon: *Compt. rend. Soc. de biol.* **67**:30, 1909.
9. Flexner, S.: *Johns Hopkins Hosp. Rep.* **6**:259, 1897.
10. Andrea: *Arch. internat. de pharmacod.* **14**:177, 1905.
11. Pearce, R. M.: *J. M. Research* **12**:329, 1904.
12. Karsner, H. T., and Aub, J. C.: *J. M. Research* **28**:377, 1913.
13. Saikowsky: *Virchow's Arch. f. path. Anat.* **34**:73, 1865.
14. Rosenbaum, F.: *Arch. f. exper. Path. u. Pharmakol.* **15**:450, 1882.
15. Athanasiu, J.: *Arch. f. d. ges. Physiol.* **74**:511, 1899.
16. Rettig, H.: *Arch. f. exp. Path. u. Pharmakol.* **76**:345, 1914.
17. Whipple, G. H.: *Bull. Johns Hopkins Hosp.* **24**:357, 1913.
18. Jobling, J. W.: Eggstein, A. A., and Peterson, W.: *J. Exper. M.* **22**:707, 1915.
19. Quinan, C.: *J. M. Research* **33**:73, 1915.
20. Sagal, Z.: *J. M. Research* **34**:231, 1916.
21. Winternitz, M. C., and Meloy, C. R.: *J. M. Research* **22**:107, 1910.
22. Loevenhart, A. S.: *Am. J. Physiol.* **6**:331, 1902.
23. Ducchieschi, V., and Almagia, M.: *Arch. ital. de biol.* **39**:29, 1903.
24. Saxl, P.: *Biochem. Ztschr.* **12**:343, 1908.

The literature on intracellular ereptase in these conditions is still more meager and contradictory. Bergell and Lewin²⁵ report that the ereptic ferment of the liver is destroyed in phosphorus poisoning. Abderhalden and Schittenhelm²⁶ on the other hand, claim that the ereptase content of the livers of phosphorus poisoned dogs is as great if not greater than that of normal dogs. In my own experiments² there was found an appreciable reduction of the power of liver extracts of phosphorus poisoned dogs to split peptone into amino-acids.

Endogenous protein metabolism in all four of the conditions mentioned is increased. Bauer²⁷ found protein metabolism in phosphorus poisoning 295 per cent. greater than normal. Very nearly identical figures were obtained by Lo Monaco²⁸ and by Ray, McDermott and Lusk.²⁹ Von Noorden³⁰ found a pathologic increase in protein metabolism in a woman poisoned with phosphorus. Other important studies based on the partition of urinary nitrogen and all indicating increased protein metabolism have been made by Badt,³¹ Münzer,³² Pfaundler,³³ Marshall and Rowntree,³⁴ Welsch,³⁵ Lusk,³⁶ Riess³⁷ and Porgess and Pribraum³⁸ in phosphorus poisoning; by Howland and Richards,³⁹ and Lindsay⁴⁰ in chloroform poisoning; and by Richter,⁴¹ Münzer³² and Riess³⁷ in acute yellow atrophy. In general, it may be said that urea excretion is decreased and ammonia excretion is increased. The increase of urinary ammonia appears to be partly the result of excessive formation of organic acids due to imperfect oxidation. For Münzer³² was able to reduce the urinary ammonia in a phosphorus poisoned animal to almost normal by the administration of sodium bicarbonate. Amino-acids, especially leucin and tyrosin, are occasionally found in the urine in phosphorus poisoning, but are usually present in acute yellow atrophy, according to the findings of Ries.³⁷

25. Bergell, and Lewin, C.: *Ztschr. f. exper. Path. u. Therap.* **3**: 1907.

26. Abderhalden, E., and Schittenhelm, A.: *Ztschr. f. physiol. Chem.* **49**:40, 1907.

27. Bauer: *Ztschr. f. Biol.* **14**:527, 1878.

28. Lo Monaco: Cited by Ray, McDermott and Lusk, Footnote 29.

29. Ray, W. E., McDermott, T. S., and Lusk, Graham: *Am. J. Physiol.* **3**:139, 1900.

30. Von Noorden, C.: *Metabolism and Practical Medicine*, London **2**:10, 1907.

31. Badt: *Diss.*, Berlin, 1891; Abstracted in *Chem. Centralbl.* **2**:265, 1891.

32. Münzer, E.: *Deutsch. Arch. f. klin. Med.* **52**:199, 1895.

33. Pfaundler, M.: *Ztschr. physiol. Chem.* **30**:75, 1900.

34. Marshall, E. K., Jr., and Rowntree, L. G.: *J. Exper. M.* **22**:333, 1915.

35. Welsch, H.: *Arch. internat. de pharmacod.* **14**:211, 1905.

36. Lusk, Graham: *Am. J. Physiol.* **19**:461, 1907.

37. Riess, L.: *Berl. klin. Wchnschr.*, **42**: 1895. Ewald Fest Number, p. 54.

38. Porgess, O., and Pribram, E.: *Arch. f. exper. Path. u. Pharmakol.* **59**:20, 1908.

39. Howland, J., and Richards, A. N.: *J. Exper. M.* **11**:344, 1909.

40. Lindsay, D. E.: *Biochem. J.* **5**:407, 1910-1911.

41. Richter: *Berl. klin. Wchnschr.*, **43**:453, 1896.

Howland and Richards³⁹ and Lindsay⁴⁰ found abnormalities in the creatinin and creatin of the urine.

That the greater part of this tissue disintegration occurs in the liver is evidenced by numerous analyses. Slowtzoff,⁴² in phosphorus poisoning, found an actual decrease in the weight of the liver in proportion to body weight from 3.6 per cent. (normal) to 2.5 per cent; the protein of the liver was reduced from 18.7 per cent. (normal) to 12.86 per cent., while the fat content was nearly double that of normal livers. Wakeman's⁴³ analyses showed that the total nitrogen of normal livers was 11.41 parts in 100 parts of dried liver substance, while in phosphorus poisoned livers it was only 7.34 parts, a loss of 35.67 per cent. The phosphorus poisoned livers also contained 37.1 per cent. less hexone bases than did normal livers. Similar but less marked changes were found by Wakeman in the livers of animals poisoned with chloroform. Porges and Pribram³⁸ also observed a reduction in the hexone bases of the liver in phosphorus poisoning. Wells⁴⁴ made chemical analyses of the liver in acute yellow atrophy and isolated and identified eight different amino-acids; the amount of soluble nonprotein nitrogen was very large; and there were small quantities of free proteoses and peptones and of xanthin and hypoxanthin.

That the liver is the source of much of the intoxication in phosphorus and chloroform poisoning and in acute yellow atrophy is evidenced by a number of facts. Thus Fischler and Bardach⁴⁵ found that dogs with Eck fistulas are more resistant to phosphorus poisoning than are normal dogs. Opie and Alford⁴⁶ showed that a carbohydrate diet, which causes an abundant deposit of glycogen in the liver, protects strongly against poisoning with phosphorus and chloroform. Graham⁴⁷ demonstrated that the resistance of dogs to the delayed toxic effect of chloroform is proportional to the amount of glycogen in the liver. Rettig¹⁶ made a similar observation in connection with phosphorus poisoning. In a previous article¹ the astonishing differences between the clinical manifestations of phosphorus poisoning in dogs with and without the feeding of sugar was emphasized. It was further shown that the livers of those animals which had received sugar contained glycogen, and that the degenerative changes

42. Slowtzoff, B.: *Biochem. Ztschr.* **31**:227, 1911.

43. Wakeman, A. J.: *J. Exper. M.* **7**:292, 1905.

44. Wells, H. G.: *J. Exper. M.* **9**:627, 1907.

45. Fischler and Bardach: *Ztschr. f. physiol. Chem.* **78**:435, 1912.

46. Opie, E. L., and Alford, L. B.: *J. A. M. A.* **62**:295, 1914; *J. Exper. M.* **21**: pp. 1 and 21, 1915.

47. Graham, E. A.: *J. Exper. M.* **21**:185, 1915.

were less marked than in those to which sugar had not been fed and whose livers contained little or no glycogen.

The source of the toxic material for which the liver appears to be responsible in these conditions is not definitely known. Van Slyke and Losee⁴⁸ concluded that the responsibility for the toxemias of pregnancy cannot be left with the amino-acids nor with the intermediate products of protein metabolism. A similar conclusion was reached by Howland and Richards³⁹ who decided that death from delayed chloroform poisoning was probably due to the presence of toxic substances of an unknown nature which owe their presence to excessive formation by abnormal processes or to the failure on the part of the organism to neutralize in the normal manner toxic substances normally formed. Schryver⁴⁹ found that the products of the incipient stage of autolysis of the liver were highly toxic.

We may now summarize the conditions found in phosphorus poisoning. There is an increased catabolism of tissue protein as evidenced by changes in the distribution of urinary nitrogen; by the occasional excretion in the urine of amino-acids, especially leucin and tyrosin; and by the frequent presence in the urine of abnormal amounts of creatin and creatinin. That the liver is the chief sufferer among the organs in this increased tissue destruction is shown by the absolute loss of weight, and the decrease of protein and protein nitrogen in the organ, and by the presence in the liver of various products of protein decomposition. There is, further, a marked increase of the fat of the liver, due in part to the unveiling of hidden or bound fat, and in part to the transport to the hepatic cells of fat which they are unable to burn. There is in addition a rapid and complete disappearance of glycogen from the liver. Finally, there is a diminution of intracellular ereptase with little or no change in the intracellular esterase.

Studies in the chemical and enzymatic changes in the liver, and of metabolism, in chloroform poisoning, acute yellow atrophy and eclampsia are not so complete as for phosphorus poisoning. But from the reports recorded in the literature, many of which have been cited, there is reason to believe that the conditions in these pathologic states are not greatly unlike those summarized in the foregoing for phosphorus poisoning. The differences are probably more quantitative than qualitative, and depend on differences in the rate at which actual necrosis of the injured liver cells takes place.

How can we correlate the foregoing conditions with the marked protective, detoxicating or antitoxic effect of a carbohydrate diet in

48. Van Slyke, D. D., and Losee: Quoted by Van Slyke, D. D., *Arch. Int. Med.* **19**:56, 1917.

49. Schryver, S. B.: *Biochem. J.* **1**:123, 1906.

poisoning with phosphorus and chloroform as has been demonstrated by Opie and Alford,⁴⁶ Graham,⁴⁷ Rettig,⁴⁸ and Simonds.⁴⁹ That the presence of a usable sugar may profoundly affect cellular metabolism was shown many years ago when Theobald Smith⁵⁰ demonstrated that the presence of an adequate supply of fermentable carbohydrate greatly reduced or even entirely inhibited the production of toxins by *B. diphtheriae* and *B. tetani*. Kendall,⁵¹ Kendall and Farmer,⁵² and Kendall, Day and Walker⁵³ have shown for a large number of different bacteria that when a fermentable carbohydrate is available, the protein of the medium is only slightly attacked, while in sugar-free mediums there is a very much greater decomposition of the protein by the bacteria. Kendall and Walker⁵⁴ found that in the presence of a fermentable sugar, *B. proteus* does not produce the extracellular enzyme which liquefies gelatin; and further that if a small amount of dextrose, up to 0.3 per cent., is present, the formation of the enzyme and the liquefying of the gelatin only begins after all of the sugar has been used up. Simonds⁵⁵ found that a culture of *B. typhosus* grown on dextrose medium showed antigenic properties and serologic reactions somewhat different from those of the same strain accustomed to growing on sugar-free mediums.

The presence of a readily available sugar also modifies the metabolism of animal cells. Indeed, the presence of a carbohydrate appears to be essential to intracellular metabolism. Landergren⁵⁶ studied protein metabolism on a diet as nearly protein-free as possible, but with sufficient calories supplied by carbohydrates. During fasting there is much breaking down of body protein. If, now, the requisite number of calories are furnished by a diet of nitrogen-free carbohydrate, endogenous metabolism is promptly decreased to an irreducible minimum. Landergren believes that there is a permanent need for carbohydrates in the body, and if these are not supplied in the diet, more protein is broken down in order to form the necessary sugar from the decomposition products of the protein. Lüthje⁵⁷ was led by his experiments to the conclusion that the presence of carbohydrate is essential for the synthesis of protein in the body from the products

50. Smith, Theobald: Tr. Assn. Am. Phys. **11**:37, 1896; J. Exper. M. **4**:373, 1899.

51. Kendall, A. I.: J. M. Research **25**:117, 1911.

52. Kendall, A. I., and Farmer, C. J.: J. Biol. Chem. **12**:13, 19, 215, 219 and 465; **13**:63, 1912.

53. Kendall, A. I., Day, A. A., and Walker, A. W.: J. Am. Chem. Soc. **35**:1201, 1913, and **36**:1937, 1914.

54. Kendall, A. I., and Walker, A. W.: J. Infect. Dis. **17**:442, 1915.

55. Simonds, J. P.: J. Infect. Dis. **17**:500, 1915.

56. Landergren, E.: Skand. Arch. f. Physiol. **14**:112, 1903.

57. Lüthje, H.: Arch. f. d. ges. Physiol. **113**:547, 1906.

of digestion of protein. Cathcart⁵⁸ also puts forward the hypothesis that the carbohydrates are absolutely essential for endocellular synthetic processes in connection with protein metabolism. Rolly⁵⁹ rendered the livers of rabbits glycogen-free by an initial dose of strychnin followed by starvation. Glycogen reappeared in the livers in very small amounts in spite of the starvation, and at the height of increased protein metabolism which accompanied the starvation. Rolly believed that this glycogen was formed from the decomposition products of the protein and that its formation is due to an effort on the part of the organism always to possess a certain amount of glycogen.

Inasmuch, therefore, as the presence of carbohydrate is of very great importance, and even appears to be essential to normal intracellular metabolism, it is all the more important that it be supplied in those conditions in which there is increased protein metabolism, as in phosphorus and chloroform poisoning, acute yellow atrophy of the liver and probably eclampsia. Indeed, in these conditions it is possible that a sort of vicious circle may be produced. Lusk⁶⁰ has shown that in phosphorus poisoning there is no sugar left in the body; and Aronsohn⁶¹ has pointed out that impoverishment of the body cells in carbohydrate and fat results in increased protein metabolism. The effect of phlorizin is to sweep the body clean of sugar. Reilly, Nolan and Lusk⁶² found that after subcutaneous injections of this drug protein metabolism may be increased 560 per cent.

What has just been said applies to the relation of carbohydrates to general metabolism. But it is the liver that shows the most serious lesions in at least three of the four conditions mentioned. And it is the liver that is one of the most important storehouses of glycogen. We are, therefore, also concerned with the local protective action of carbohydrate on the liver itself. Mathews⁶³ has given reasons which make it probable that glycogen is stored in the liver primarily for the benefit of the liver itself, and that it is only incidentally liberated as glucose when it is demanded by the other tissues of the body. That the presence of an abundant supply of glycogen in the liver does exert a local protective action is evidenced (1) by the effect on intracellular enzymes, as shown by Simonds (Footnotes 1 and 2); and (2) by the entire absence or greater mildness of the lesions in the livers of sugar fed, phosphorus poisoned dogs, as compared with nonsugar fed, phos-

58. Cathcart, E. P.: *Jour. Physiol.* **39**:311, 1909-1910.

59. Rolly, Fr.: *Deutsch. Arch. f. klin. Med.* **83**:107, 1905.

60. Lusk, Graham: *Am. Jour. Physiol.* **1**:5, 1898.

61. Aronsohn, Ed.: *Ztschr. f. klin. Med.* **61**:153, 1907.

62. Reilly, F. H.: Nolan, F. W., and Lusk, Graham: *Am. J. Physiol.* **1**:395, 1898.

63. Mathews, A. P.: *Physiological Chemistry*, New York, p. 786, 1915.

phorus poisoned dogs as shown by Opie and Alford,⁴⁶ Rettig¹⁰ and Simonds.¹

In its mechanism this local protective action may involve several factors. In the first place, the metabolism of the liver itself is increased. The presence of a supply of carbohydrate ready at hand spares the protein of the hepatic cells. Whipple and Hooper⁶⁴ have shown that the feeding of carbohydrates stimulates the excretion of bile in bile-fistula dogs. It is not impossible that the same applies to other functions of the liver cells and that the presence of an adequate supply of sugar will stimulate these cells to increased function and will render them more resistant to the injurious action of the poison.

It is Wells' view⁶⁵ that in chloroform and phosphorus poisoning there is an interference with the oxidative processes in the liver, and that this accounts for the accumulation of fat in this organ in these conditions. Lusk⁶⁶ failed to find any reduction in oxidations in the body in phosphorus poisoning so far as general metabolism is concerned. Ducceschi and Almagia⁶⁷ found no reduction in the oxidizing enzyme aldehydase in phosphorus poisoned livers. Joannovics and Pick,⁶⁸ however, think that the interference by chloroform with oxidation in the liver is probably a selective one, and that one or more, but not all, of the manifold vitally important oxidative processes of the liver are put out of commission by the narcotic. Slowtsoff⁴² claims to have found less peroxidase in the livers of phosphorus poisoned animals.

Reduced oxidation in the body in phosphorus poisoning is further indicated by the presence of organic acids, especially lactic acid, in the urine as observed by Araki,⁶⁹ Hauser,⁷⁰ Riess,³⁷ and Mandel and Lusk.⁷¹ In a study of the respiratory exchange in phosphorus poisoning Scheider⁷² found a 26 per cent. decrease in the excretion of carbon dioxide; while Welsch³⁵ found a 11 to 20 per cent. decrease.

The observations just cited indicate that there is a condition of reduced oxidation in the body in phosphorus and chloroform poisoning. But this does not necessarily mean that this is due to such a reduction in the ability of the body to carry on its oxidative processes as has been supposed. The reduced oxidation may be due in part to

64. Whipple, G. H., and Hooper, C. W.: *Am. J. Physiol.* **40**:349, 1916.

65. Wells, H. G.: *J. A. M. A.* **46**:341, 1906.

66. Lusk, Graham: *Science of Nutrition*, Philadelphia, 1909.

67. Ducceschi, V., and Almagia, M.: *Arch. di farmacol. sperim.* **2**:1, 1903.

68. Joannovics, G., and Pick, E. P.: *Arch. f. d. ges. Physiol.* **140**:327, 1911.

69. Araki, T.: *Ztschr. f. physiol. Chem.* **17**: 1893.

70. Hauser, A.: *Arch. f. exper. Path. u. Pharmakol.* **36**:165, 1895.

71. Mandel, A. R., and Lusk, G.: *Am. J. Physiol.* **16**:129, 1906.

72. Scheider: *Dissertation, Würzburg*, 1895. Cited by Loewi: *v. Noorden's Metabolism in Practical Medicine*, London, 1907, p. 1108.

the depletion of the supply of readily oxidizable material. That the glycogen in the liver at the time of poisoning is at least partially oxidized is evident from the fact, noted by Laub,⁷³ Walko,⁷⁴ Neubauer,⁷⁵ and others, that in spite of the very rapid glycogenolysis, there is only very exceptionally a hyperglycemia or glycosuria. Neubauer and Porges⁷⁶ even found a hypoglycemia in phosphorus poisoning. Neubauer⁷⁶ distinguishes between two groups of conditions in which glycogen disappears from the liver. In one group the glycogen is used up because of increased need, as in starvation, muscular work, fever, etc. In this group, to which phosphorus poisoning belongs, hyperglycemia and glycosuria do not occur. In the second group, the glycogenolysis is the result of nervous stimuli, as after stimulation of the splanchnics, injection of epinephrin, and possibly after poisoning by phlorizin. In these cases, hyperglycemia and glycosuria do occur.

It is frequently stated that the deposit of fat and of glycogen in the liver results from the same general cause, namely, reduced oxidation. Rosenberg⁷⁷ and Rosenfeld,⁷⁸ however, found evidence of antagonism between glycogen and fat. Mathews⁷⁹ takes the view that glycogen is stored in the liver at a time when the portal blood is relatively rich in oxygen; that is, during digestion, and that it tends to disappear when, during the fasting period, the oxygen content of the portal blood is very low. This view is supported by the observation of Araki⁸⁰ that glycogen of the liver is reduced in carbon dioxid poisoning. There is reason to believe that the primary object of the supply of stored glycogen is to enable the liver to function properly in the presence of very little oxygen (Mathews). The work of Embden and Wirth⁸¹ shows that the liver can burn its own glycogen more readily than it can oxidize glucose or a number of other organic substances supplied to it. Rettig¹⁶ is of the opinion that the primary effect of phosphorus is not a direct toxic injury to the cells, but that it is the result of the absence of easily oxidizable carbohydrate.

Mathews⁸² has advanced the hypothesis that intracellular respiration is a splitting off of water from the cytoplasm and its dissociation

73. Laub, M.: *Wien. klin. Wchnschr.* **10**:27, 1898.

74. Walko, K.: *Ztschr. f. Heilk.* **22**:8, 1901.

75. Neubauer, E.: *Arch. f. exper. Path. u. Pharmacol.* **61**:387, 1909.

76. Neubauer, E., and Porges, O.: *Biochem. Ztschr.* **32**:290, 1910.

77. Rosenberg, O.: *Ziegler's Beitr. z. path. Anat. u. z. allg. Path.* **49**:284, 1910.

78. Rosenfeld, G.: *Allg. Med. Central-Ztg.*, 1897; *Ergebn. d. Physiol.* **1**:650, 1901.

79. Mathews, A. P.: *Physiological Chemistry*, New York, 1907, p. 786.

80. Araki, T.: *Ztschr. f. physiol. Chem.* **19**:422, 1894.

81. Embden, G., and Wirth, J.: *Biochem. Ztschr.* **37**:1, 1910.

82. Mathews, A. P.: *Biolog. Bull.* **8**:331, 1905.

with the liberation of nascent hydrogen and oxygen. This nascent oxygen accomplishes the oxidative processes within the cell. The hydrogen is disposed of by combining either with atmospheric oxygen, if this is present (aerobic respiration), or, if this is absent, with some other available easily oxidizable substance (anaerobic respiration). According to this hypothesis, the atmospheric oxygen absorbed in the lungs and circulating in the blood, merely acts as a depolarizer to take care of the nascent hydrogen. Any other substance which can easily combine with the hydrogen will serve the purpose of the atmospheric oxygen and permit respiration to go on in the absence of air. Mathews⁸³ further points out that while carbohydrates are readily oxidized and thus act as reducing agents, they are also reduced without difficulty and may act as oxidizing agents. By means of this property of being easily reduced, they play an important part in anaerobic respiration. Packard⁸⁴ has shown that those carbohydrates which can be absorbed when injected into the peritoneum of the common minnow (*Fundulus heteroclitis*) greatly increase its resistance to lack of oxygen. It has been shown many times that perfused organs will retain their vitality for a much longer time if the perfusion liquid contains glucose.⁸⁵ It is not an unreasonable supposition, therefore, that an adequate supply of readily oxidizable glycogen will help to maintain the oxidative activity of the liver in the presence of interference within intracellular oxidations due to phosphorus and chloroform poisoning.

The contents of the hepatic and other cells of the body are colloidal in nature. Some of the degenerative changes occurring in cells may be explained on the basis of reversible colloids. Certain substances, among them glycogen and the sugars, have a protective action and tend to prevent the "breaking" of emulsions and the precipitation of colloids. Fischer⁸⁶ lays great emphasis on this protective action of glycogen in the liver in phosphorus poisoning. The local reduced oxidation results in the accumulation of acids in the liver. These cause the cells to take up water which "breaks" the emulsion and droplets of fat appear. The presence of abundant glycogen, however, stabilizes the emulsion and prevents fatty degeneration, which, according to Fischer, is a purely physicochemical phenomenon governed by physicochemical laws.

Not only do certain colloids protect others from precipitation, but the permeability of colloids can be modified by various means.

83. Mathews, A. P.: *Physiological Chemistry*, New York, 1915, p. 41.

84. Packard, W. H.: *Am. J. Physiol.* **18**:164, 1907, and **21**:310, 1908.

85. Locke, F. S.: *J. Physiol.* **31**:13, 1904, and *Centralbl. f. Physiol.* **14**:670, 1901.

86. Fischer, M. H.: *Fats and Fatty Degeneration*, New York, 1917, p. 74.

Bechhold and Ziegler⁸⁷ found that glucose retarded the diffusion of some substances into gels. It is not fully known in just what condition phosphorus reaches the liver to exert its toxic effect. Plavac⁸⁸ has studied this point particularly, and concluded that the phosphorus enters into some combination, and that this compound acts as a poison instead of the phosphorus being resorbed and circulating and acting as such. In whatever form the phosphorus finally reaches the liver, it appears probable that it will find the cells less permeable if they are amply supplied with glycogen.

In a previous paper¹ it was shown that the feeding of sugar increases the esterase content of the livers of both normal and phosphorus poisoned animals. In those animals poisoned with phosphorus and fed with sugar in large amounts the livers contained much glycogen, and showed less fatty change than the nonsugar fed control animals. It was suggested that the relatively small amount of fat in the livers of the sugar fed animals was in some way closely related to the marked increase of the esterase.

The metabolism of fats is not yet fully understood, but it is probable that the intracellular lipases synthesize fat in the cells from materials brought to them by the circulating fluids. Hanriot⁸⁹ observed such synthesis *in vitro* in the case of butyric acid and glycerol which formed monobutylin under the influence of lipase; and Pottevin⁹⁰ succeeded in synthesizing triolein. Bradley,⁹¹ it is true, studied the lipase content of different tissues in relation to the amount of fat which they contained and found no parallelism between the two. He concluded from this that lipase does not synthesize fat. Bayliss,⁹² however, has presented reasons why this observation of Bradley's does not negative the hypothesis of the synthesis of fat by lipase.

Wells⁹⁵ is of the opinion that in the presence of the inhibition of oxidation in the liver cells in phosphorus poisoning the lipase synthesizes fat, and he thus accounts for the accumulation of fat in this organ in phosphorus and chloroform poisoning. The finding of the writer¹ that there is no reduction in the esterolytic activity of the liver in phosphorus poisoning harmonizes with this view. On the other hand, the observation recorded in the same paper,¹ that the feeding of sugar increases the hepatic esterase in phosphorus poisoned dogs and that the livers of these sugar fed animals showed less fatty change than did the controls, seems, at first sight, to be contradictory. Rosen-

87. Bechhold, H., and Ziegler, J.: Ztschr. f. physikal. Chem. **56**:105, 1906.

88. Plavac, V.: Arch. f. ges. Physiol. **104**:1, 1904.

89. Hanriot, M.: Compt. rend. Soc. de biol. **132**:212, 1901.

90. Pottevin, H.: Compt. rend. Soc. de biol. **136**:767, 1903.

91. Bradley, H. C.: Jour. Biol. Chem. **13**:407, 1913.

92. Bayliss, W. M.: Nature of Enzyme Action, New York, 1914, p. 53.

feld⁹³ claims that a deficiency of carbohydrate in the diet is the essential condition to the deposit of fat in the body. Rosenberg⁷⁷ and also Rosenfeld⁷⁸ noted "a certain antagonism" between fat and glycogen. Rosenberg⁷⁷ observed that in fatty degeneration the cells were poor in glycogen, and that if glycogen were supplied the fatty degeneration diminished or disappeared. Lusk³⁶ concluded that as a result of the depletion of the glycogen of the liver in phosphorus poisoning the "sugar hungry" cells attract fat in greater quantity than they can burn.

In the oxidation of fats in the body it is probable that they are first hydrolyzed by the intracellular lipases. With the "sugar hungry" cells attracting an augmented amount of the crude materials from which fat is synthesized, the equilibrium point for the activity of the lipase would be well toward the side of synthesis. The hydrolysis and subsequent oxidation of fats within the cells would therefore be interfered with. The presence of easily oxidizable glycogen in the liver cells reduces the demand for fat, so that the equilibrium point would not be disturbed by the attraction of an excessive supply of raw materials.

The changes occurring in the liver in phosphorus poisoning have been very generally charged to the process of autolysis. Thus Jacoby⁹⁴ found that autolysis was very much more rapid in the livers of phosphorus than in normal dogs. Wells⁶⁵ concluded that chloroform, phosphorus and possibly other poisons stop cell activity, leaving the autolytic enzymes free to digest the necrosed cells. Jackson and Pearce,⁹⁵ and Frank and Isaac,⁹⁶ however, call attention to certain differences in the chemical processes occurring in a liver undergoing rapid or immediate necrosis and those accompanying "slow degeneration, as in phosphorus poisoning." They believe that although investigation on the livers of phosphorus poisoned animals tends to show that the change is an autolysis in which amino-acids are split off from the protein molecule, it is not of the same type as that occurring in a completely necrotic cell. That there is some justification for this differentiation is evident from a comparison of the results of chemical analyses obtained by Jackson and Pearce⁹⁵ in liver necrosis, due to injection of hemolytic immune serum, and by Wells⁴⁴ in acute yellow atrophy of the liver, with the results of chemical analyses by Wake-man⁴³ in phosphorus and chloroform poisoning, and by Wells⁹⁷ in chloroform poisoning.

93. Rosenfeld, G.: Berl. klin. Wchnschr. 43:978, 1906.

94. Jacoby, M.: Ztschr. f. physiol. Chem. 30:174, 1900.

95. Jackson, H. C., and Pearce, R. M.: J. Exper. M. 9:520 and 554, 1907.

96. Frank, E., and Isaac, S.: Arch. f. exper. Path u. Pharmakol. 64:274, 1910.

97. Wells, H. G.: Arch. Int. Med. 1:589, 1908.

From the standpoint of the treatment of these conditions this is a most important distinction. For as Wells⁶⁵ suggests, if enough liver cells have been destroyed, hepatic insufficiency may cause death. The logical desideratum in treatment will therefore be to prevent the "slow degenerative process" from going on to actual necrosis.

It appears, furthermore, that the amount of glycogen in the liver in some way affects the rate of autolysis in that organ. The liver in phosphorus poisoning is free of glycogen, and as already mentioned, Jacoby⁹⁴ and others have shown that the livers of such animals undergo very rapid autolysis. Schryver⁹⁸ found that the autolytic processes were greatly accelerated in the livers of animals which had been given thyroid extract. Kuriyama⁹⁹ observed that the feeding of thyroid extract caused a rapid disappearance of glycogen from the liver. This may explain Wells¹⁰⁰ failure to find any increase in autolysis when thyroid extract was added to autolyzing liver *in vitro*. Furthermore, Bradley¹⁰¹ found that of the three types of muscle tissue, the striated form autolyzed most slowly, while heart and smooth muscle autolyzed from 50 to 100 per cent. more rapidly than did the skeletal muscle. In this connection Cremer's¹⁰² analyses of the glycogen content of the different forms of muscle are of special significance. Cremer found 1.85 per cent. glycogen in skeletal muscle and 0.12 per cent. in heart muscle. Starvation also frees the liver of glycogen. Lane-Claypon and Schryver¹⁰³ found that not only was the latent period in autolysis much shorter in the livers of starved cats than in the livers of cats on the usual diet, but that the degradation of the protein was much more rapid and complete.

Mention has already been made of the increased protein metabolism in phosphorus and chloroform poisoning. In this connection it is significant that, as shown by the analyses of Bauer,²⁷ Münzer,³² Marshall and Rowntree,³⁴ Howland and Richards³⁹ and others, the increased protein metabolism does not become manifest until the second or third day—that is, until the liver is free from glycogen. That this latent period is not due entirely to the slowness in absorption of the phosphorus is evident from the fact that it is the poison which causes the using up of the glycogen in the liver. Attention may here be called again to the similarity between the effect of diminished oxygen supply and phosphorus poisoning as pointed out by Bauer,²⁷

98. Schryver, S. B.: J. Physiol. **32**:159, 1905.

99. Kuriyama: Am. J. Physiol. **43**:481, 1917.

100. Wells, H. G.: Am. J. Physiol. **11**:35, 1904.

101. Bradley, H. C.: Jour. Biol. Chem. **33**:11, 1918.

102. Cremer, A.: Ztschr. f. Biol. **24**:75.

103. Lane-Claypon, J. E., and Schryver, S. B.: J. Physiol. **31**:169, 1904.

Loewi,¹⁰⁴ Wells⁶⁵ and others. Loewi has tabulated the similarities in parallel columns. Terray¹⁰⁵ found that the increased nitrogen output does not occur immediately after the oxygen supply is reduced, but on the succeeding days.

In a previous paper² it was shown that the creptic power of the liver was reduced in phosphorus poisoning and that the feeding of sugar prevented a decrease but did not cause any increase of this ferment. The function of the intracellular creptase is not fully understood. However, since Vernon¹⁰⁶ found it present in the cells of all of the organs of the body, it appears probable that it is concerned in intracellular metabolism, most likely serving to synthesize amino-acids into peptones. Synthesis has not been satisfactorily demonstrated *in vitro* for any of the proteolytic ferments. Both Oppenheimer¹⁰⁷ and Cohnheim¹⁰⁸ question the assignment of a reversible reaction to the proteoclastic enzymes. But Bayliss¹⁰⁹ has made it clear that "although the direct evidence on the subject of protein synthesis is at present meager, the phenomena seen in trypsin digests are quite what would be expected if equilibrium in a reversible reaction be the explanation of what takes place. Such phenomena are (1) retardation due to accumulation of the products of the reaction, (2) recommencement of a reaction which had apparently come to an end, if the products be removed by dialysis, or other means, or if their concentration be reduced by dilution." The work of Folin¹¹⁰ also supports the belief that the intracellular creptase synthesizes protein from the amino-acids absorbed from the digestive tract.

Van Slyke and Meyer¹¹¹ have shown that amino-acids disappear very rapidly from the blood during digestion, being taken up and temporarily fixed by the tissues. Living cells do not normally contain demonstrable amounts of peptone. Hence the equilibrium point in the living cell is well on the side of the synthesis of amino-acids into peptone. Furthermore, the same cells contain tryptase and peptase,¹¹² so that any peptone synthesized by the creptase would be further synthesized into protein by the associated intracellular enzymes. Furthermore, since the actual demand for nitrogen by the body is relatively small, the total amount of synthesis will not be great, the

104. Loewi, O.: v. Noorden's Metabolism and Practical Medicine, London, 1907, p. 1128.

105. Terray: Arch. f. d. ges. Physiol. 65:397, 1897.

106. Vernon, M. H.: Jour. Physiol. 33:81, 1905.

107. Oppenheimer, C.: Die Fermente und ihre Wirkungen, Leipzig, 1910, Ed. 3, p. 281, etc.

108. Cohnheim, O.: Enzymes, New York, 1912, p. 90.

109. Bayliss, W. M.: Nature of Enzyme Action, New York, 1914, p. 69.

110. Folin, O.: J. A. M. A. 63:823, 1914.

111. Van Slyke, D. D., and Meyer, G. M.: J. Biol. Chem. 12:399, 1912.

112. Vernon, M. H.: Intracellular Enzymes, London, 1908, and Dochez, A. R.: J. Exper. M. 12:666, 1910.

major portion of the amino-acids temporarily stored being ultimately eliminated as urinary nitrogen. It is only when the stored amino-acids of the tissues are exhausted by starvation or by increased metabolism, as in phosphorus poisoning, that the equilibrium point is displaced to the side of intracellular proteolysis and peptolysis. There is in addition, in prolonged starvation and in phosphorus poisoning, a disappearance of the glycogen with removal of its inhibiting action on the autolytic ferments, which results in a still more vigorous breaking down of the protein of the body, partly for the purpose of furnishing carbohydrate for the "sugar hungry cells."

Hence, it would appear that under normal conditions the function of ereptase is to synthesize amino-acids into peptones. In phosphorus and chloroform poisoning, in acute yellow atrophy and perhaps in eclampsia, changes occur in the liver of the nature of autolysis, or a modified autolysis in the sense of Jackson and Pearce.⁹⁵ There are thus liberated substances on which ereptase exerts its disintegrative power. This explains the not infrequent finding of amino-acids, especially leucin and tyrosin, in the urine in phosphorus and chloroform poisoning, and their almost constant presence in acute yellow atrophy (Riess³⁷).

Schryver,¹¹³ who observed that the livers of starved animals autolyzed more promptly and more rapidly than did the livers of fed animals, has advanced the interesting idea that the liberation and activation of the autolyzing enzymes in the cells during life is a normal mechanism whose function it is to protect the organism against starvation. These enzymes come into action only when the energy needs of metabolism are not satisfied by the foodstuff ingested. Cohnheim¹¹⁴ has pointed out certain alleged differences between the products of digestion by autolytic enzyme and by erepsin. It would seem that the autolytic process can be more easily explained as the result of the interaction of several enzymes. Ereptase is only one of the ferments concerned. Ereptase is unable to affect unchanged protein. In a considerable series of unpublished experiments it was found that extracts of livers which split peptone into amino-acids with ease produced no measurable proteolysis of horse or dog serum either with or without a preliminary treatment of the serum with chloroform according to the method of Jobling and Peterson.¹¹⁵ Hence it would seem that in phosphorus and chloroform poisoning and probably in acute yellow atrophy and eclampsia, the normal activity of the intracellular enzymes, including ereptase, is reversed.

113. Schryver, S. B.: *Biochem. J.* **1**:123, 1906.

114. Cohnheim, O.: *Ztschr. f. physiol. Chem.* **35**:134, 1902.

115. Jobling, J. W., and Peterson, W.: *J. Exper. M.* **19**:459, 1914.

SUMMARY AND CONCLUSIONS

In phosphorus poisoning there is a rapid disappearance of glycogen from the liver. Beginning about the time of the disappearance of the glycogen, there occur fatty degeneration and infiltration of the liver, increased protein metabolism, and decreased oxidation. In addition there is a reduction of the intracellular ereptase with little or no change in the esterase content of the liver.

The feeding of sugar to phosphorus poisoned animals conserves and replenishes the hepatic glycogen and markedly diminishes the toxic effect of the phosphorus as shown by the mildness of the clinical symptoms, by the continued presence of glycogen in the liver, and by the very moderate degree of degenerative changes in that organ. The available data in the literature on the chemical, enzymatic and metabolic changes in chloroform poisoning, acute yellow atrophy and in eclampsia, are not so complete as for phosphorus poisoning, but from the facts at hand there is reason to believe that the differences are more quantitative than qualitative, and that the administration of sugar in these three conditions will have something of the same protective effect as in phosphorus poisoning.

An attempt has been made to arrive at some understanding of the mechanism of this protective action of sugar, or more correctly, of the conservation and replenishing of the supply of glycogen of the liver, in poisoning with phosphorus. It has been suggested that an adequate supply of glycogen may affect the state of the colloids of the cell, (1) by stabilizing the emulsion and preventing its "breaking" with the throwing out of droplets of fat; and (2) by reducing the permeability of the cells to the poison.

From studies of the literature there is reason to believe that a certain amount of carbohydrate is essential to normal protein metabolism. If it is not supplied in the diet it is obtained by increased breaking down of protein.

In phosphorus poisoning there is a diminution of the power of the body to carry on its normal oxidative processes, and, at the same time, there is an increased demand for readily oxidizable material. Fat cannot satisfactorily supply this augmented need in the presence of the reduced oxidizing power, because fat is twice as difficult to oxidize as carbohydrate. An attempt is made to meet this increased demand on the part of the liver by the transportation to it of fat which it is unable to burn, and by increased protein metabolism. It has been shown that the liver is able to burn its own glycogen more readily than glucose or many other substances supplied to it.

Many of the changes occurring in phosphorus poisoned livers are of the nature of an autolysis. The presence of glycogen in the liver appears to inhibit the autolysis of this organ *in vitro*, because it has been shown that autolysis begins more promptly, proceeds more rapidly and brings about a more complete degradation of the protein molecule in those livers which have been previously rendered glycogen-free by starvation of the animal, or by poisoning with phosphorus, or by the administration of thyroid extract.

It is believed, further, that the autolysis occurring in phosphorus poisoned livers is the result of a reversed action by those intracellular enzymes which normally carry on the synthetic processes in protein metabolism. On account of changes within the cell, possibly the result of reduced oxidation, the equilibrium point in the enzyme reaction is displaced, and the normal function of the enzyme reversed.

The conservation and replenishing of the glycogen of the liver by the administration of sugar is believed, therefore, to protect the animal against phosphorus poisoning (1) by its effect on the colloids of the cell; (2) by furnishing carbohydrate which appears to be essential to the normal synthetic processes of protein metabolism; (3) by supplying the most easily oxidizable material to an organ whose oxidizing power has been reduced by the poison; (4) by inhibiting the process of autolysis *in vivo*; and (5) by preventing the reversal of the action of the intracellular enzymes.

It is believed that the facts here presented are sufficiently well substantiated to justify the opinion that the administration of sugar will prove to be an important therapeutic measure in phosphorus and chloroform poisoning in humans, in acute yellow atrophy of the liver, and, possibly, in eclampsia.

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EXPERIENCES WITH A RECENT EPIDEMIC OF MENINGOCOCCIC MENINGITIS AMONG A CHINESE CIVIL POPULATION *

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During the past spring and early summer (1918) a study was made of an epidemic of meningococcic meningitis occurring among a civil population in a district in South China. Some of the results of the investigation have proved of sufficient interest to warrant their somewhat detailed description, in the hope that they may be of value to the medical officers of the Army and Navy combating epidemic meningitis.

GENERAL DESCRIPTION

The beginning of the epidemic is obscure. An epidemic of meningococcic meningitis heretofore among the Southern Chinese is practically unknown. Hence, when the first cases occurred, the proper diagnosis was not made. It was not until the second week in February that cases which were regarded previously as hemorrhagic smallpox were definitely diagnosed as epidemic meningitis. From that time until the first of June there were reported officially, 1,041 cases; but it is estimated that, including the "missed" cases, the actual number was nearer 2,500. Among the cases reported the mortality was 85 per cent. The epidemic continued until the first week of July; the largest number of cases occurred in March.

The source of infection is likewise indefinite. Although no epidemics have occurred in this district, yet it is reasonable to assume the occurrence of sporadic cases now and then. Indeed, there is a case on record which appeared five years ago. Again, in the Philippine Islands, which are on a direct trade route, there were reported about three years ago seventy cases, of which some yielded pure spinal cultures of the meningococcus. Furthermore, this district is a great gateway to the southern part of the Orient, and enormous numbers of persons pass through it; undoubtedly some are carriers of meningococci.

The locality has points of interest with reference to epidemic meningitis. In the first place, it is situated in the subtropical zone bordering on the tropical. In view of the extent of the epidemic, it becomes problematical whether this disease is one of the temperate

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zone. In the second place, the district is greatly overcrowded,¹ and in some quarters there exist living conditions quite analogous to those found in an overcrowded camp. Again, the population comprises for the most part poor people, passively resisting western methods, so that the epidemic was disseminated thickly on a good soil.

OBSERVATIONS ON TREATMENT

The following observations were made at a local hospital where none but Chinese were received. They are based on a total number of 417 patients. At this point it may be stated that in certain sections of China conservatism is still very strong and modern medicine is not favorably entertained. Hence the following statistics offer a sad but interesting study:

One hundred and four patients received neither serum treatment nor lumbar puncture. Of these, 84.6 per cent. died. This mortality corresponds with the general death rate for the disease throughout the district.

In 346 patients lumbar puncture was made from once to five times. Of these 54.1 per cent. died.

In 71 patients, lumbar puncture combined with the spinal injection of antimeningococcic serums having a low antibody content, was made. Of these, 45 per cent. died. These serums were on hand before my arrival.

(Taking at random 10 spinal cultures isolated from local cases, one serum agglutinated 5 of them, but 3 other specimens agglutinated from 2 to 3, usually in dilutions of 1:50. Flexner serum used as a control agglutinated 56 out of 59 similar cultures and usually in dilutions of 1:800.)

Several conclusions may be drawn from these records. First, the mortality is appalling when no treatment is given. Second, spinal tapping by itself, while showing an improvement in the death rate, is still far from a satisfactory therapeutic procedure. Third, the injection of a serum poor in quality offers only slightly better hope. Lastly, a serum low in agglutinin content is apt to be therapeutically ineffective.

When these methods of treatment are compared with the results recently obtained in civil and military practice by proper antimeningococcic serotherapy, it is certain that the employment of the latter is indicated at all times.

1. The area of the district is 390 square miles. The official population is 535,100 and the population to the square mile 1,372. But 300,000 of these Chinese live in a small section of this area—a section about 3 miles long and one-half mile wide.

BLOOD CULTURE STUDIES

At present an extensive literature is being reported on the appearance of the meningococcus in the circulating blood. It is stated that the organism appears very early in the course of the disease. On this account the following blood cultures should prove of interest. Owing to certain difficulties no selection of cases could be made, but in this series of ten cases it happened that all were moribund, and in some instances the blood culture was made in the agonal period.

The blood cultures were made by inoculating from 2 to 3 c.c. of whole blood into each of two flasks containing 100 c.c. of veal infusion, 1 per cent. dextrose broth of 0.7+ acidity (phenolphthalein). Besides these flasks, about four or five plates of dextrose agar were poured, each containing 2 c.c. of blood. None of the plates was positive; a positive result was usually indicated by growth in one or both flasks. All cultures thus obtained were tested for type and corresponded with the spinal strain—the parameningococcus in all instances, as I will describe later.

Case 1, from whose spinal fluid parameningococci were isolated, was cultured on the fourth day of illness. The patient died two days later. The blood culture was negative.

Cases 2, 5, 6, 8 and 9 yielded no growth from the spinal fluids (except Case 2), but the appearance of the fluids was typical and they contained many gram-negative diplococci, intracellular and extracellular.

The five patients died two days after obtaining the culture, which was taken on the fifth day of illness, except in Case 6, when it was taken on the second day of illness. The cultures were negative in all cases.

In Cases 3 and 4 the patients were comatose on the fifth day of illness, when the culture was taken. They died the following day. The blood as well as the spinal fluid showed a growth of meningococci.

Cases 7 and 10 were similar in detail to Case 3, except that there was no coma or petechial rash, but death occurred the day following the taking of the culture, which was positive.

From these cases one observes that of the ten patients, four yielded positive blood cultures, but of the latter all died one day later. It is difficult to interpret the small number of findings; and the evidence is too scant to indicate whether the infection was primary or secondary in the blood in these cases. The specimens were taken antemortem and could be explained as antemortem meningococcal invasions of the blood. However, the results served to emphasize the desirability of intravenous therapy.

THE PREVAILING TYPE OF MENINGOCOCCUS AMONG PATIENTS

Spinal cultures in a pure state were obtained from 60 patients. Fifty-nine of the patients were examined at the height of the epidemic. Of these, 56 were para types and 3 irregular para types. The para type when tested corresponds with Type I of Gordon's (English) classification; the normal, with Type II; and the irregular para possibly with Type III. The para type agglutinations ranged from 1:50 to 1:800; the irregular para types showed the reactions in Table 1.

TABLE 1.—REACTIONS SHOWN BY IRREGULAR PARA TYPES

Culture Number	Normal Type Immune Serum	Para Type Immune Serum	Polyvalent Serum
021	1:50	1:400	1:800
030	1:100	1:400	1:400
052	1:50	1:200	1:200

From this we conclude that during the height of the epidemic almost 95 per cent. of the patients were infected by the same type of meningococcus, the para type.

The remaining case of the sixty patients examined occurred during July when the epidemic was on the wane and the incidence of the disease in a given section was relatively infrequent. It was remarkable that this patient should yield a normal or regular type meningococcus.

In this connection it is interesting to note that two of the cultures isolated three years previously in the Philippine epidemic were tested and found to be para types. Also an epidemic of meningitis in a city along the trade route from this district and occurring somewhat later, yielded nineteen para types out of twenty spinal cultures isolated. The inference is that during the height of the epidemic almost all the patients were infected with one type, the parameningococcus.

BACTERIOLOGIC STUDIES ON CARRIERS

(a). *Contact Carriers*.—No extensive work could be done on contact carriers at the height of the epidemic, as I arrived at the time of its subsidence. I shall, however, discuss the results obtained then by the local bacteriologists who made several cultures.

These cultures were made as routine examinations of contacts with patients for the presence of the meningococcus in the nasopharynx. It appears that the work was very carefully done; only a few cultures were examined at a time and all plate cultures contaminated with saliva were discarded. The criteria for the recognition of the meningococcus were (1) typical colony morphology, (2) absence of pigment, (3) acid production in dextrose and maltose and not in saccharose medium.

(4) typical morphology by Gram's stain, (5) ready emulsification of the growth of subcultures. No agglutination tests were made, however. Sheep serum water (1 part serum to 2 parts water) 20 per cent., agar was used for the plate cultures.

Examining once only contacts of several patients, it was found that:

71 Europeans	yielded 7 carriers (9.8 per cent.)
133 Chinese	yielded 9 carriers (6.7 per cent.)
<hr/>	
204 examined	yielded 16 carriers (7.8 per cent.)

The ratio of incidence of meningitis among the Europeans to the white population of the district was as 1 is to 1,250; in the case of the Chinese to the colored population as 1 is to 212 (if 2,500 is used as the basis for the number of cases). These cultures were taken at the height of the epidemic; the number of contact carriers in both series is lower than is usually the case.

One deduction, however, can be made, namely, that the carriers were more prevalent among the white population, notwithstanding the fact that very few of the latter were afflicted (4 to 2,500 of Chinese).

(b). *Noncontact Carriers.*—As no opportunity presented itself to continue the study of contact carriers, my attention was paid to a class which may be regarded only nominally as noncontact carriers. In the event of an epidemic of so great an extent as this one, a group can hardly be chosen as a representative noncontact class. It was finally decided that a local jail, in which no case of epidemic meningitis developed throughout the epidemic, would offer a suitable source for the determination of the number of carriers for comparative study.

In interpreting the results, these factors should be considered: The prisoners were in the main previous residents of the district. There was a daily average of 600 inmates. The length of confinement before the cultures were taken varied from a few days to several years. The prisoners were kept isolated in individual, well ventilated cells; there was no overcrowding. In brief, the sanitary conditions in the jail were better than in a great part of the Chinese community.

The following cultures were made on unlaked sheep blood, veal infusion agar with 1 per cent. dextrose (defibrinated blood 1 part, agar 15 parts). The cultures were taken from the nasopharynx with a West swab, care being taken to avoid contamination with saliva. The plates, each person's culture on a single plate, were incubated immediately after inoculation.

The total number of Chinese prisoners swabbed was 151
Plate cultures contaminated with saliva and there-
fore discarded were..... 21

A. Negative Cultures

1. Plate cultures showing no suspicious colonies.... 74
 2. Those showing suspicious colonies which failed to grow characteristically..... 19
 3. Those showing suspicious colonies which were proven negative by agglutination ("flavus agglutination") 3
 4. Those showing suspicious colonies which subsequently grew at room temperature..... 2
- Thus making a total of 98 negative cultures.

B. Positive Cultures

1. Plate cultures showing typical colonies, consisting of gram-negative diplococci of characteristic morphology, but which failed to grow on subculture. There were usually two or three colonies transplanted. On the basis of previous experience it was thought proper to include these with the positive cultures. They were as shown in Table 2.

TABLE 2.—PLATE CULTURES SHOWING TYPICAL COLONIES

Serial Number	Age (Years)	Time in Jail	Degree of Infection*
7	20	1 mo.	±
46	25	2 mos. 9 days	+
70	30	2 mos.	±
97	27	1 mo. 5 days	±
132	28	5 mos. 14 days	±

* The term "degree of infection" is used to signify the relative number of colonies in the plate cultures. This gives an indication as to the extent of the infection of the nasopharynx. Hence ± signifies an occasional colony; +, few colonies; ++, numerous colonies of meningococci, but other organisms predominating; +++ meningococcus colonies predominating; and +++++, a pure culture of the meningococcus.

2. Plate cultures showing typical colonies consisting of gram-negative diplococci of characteristic morphology; producing acid in dextrose and maltose, but not in saccharose medium; showing no growth at room temperature, but a typical growth on subculture (ready emulsification, no pigment, mucoid, etc.); showing no agglutination in saline or normal horse serum (1:50) controls, and no agglutination with type or polyvalent antimeningococcic serum (Table 3).

TABLE 3.—PLATE CULTURES SHOWING INAGGLUTINABLE CULTURES

Serial Number	Age (Years)	Time in Jail	Degree of Infection
56	31	2 mos. 7 days	++
75	27	14 days	+
76	30	11 days	++
100	22	2 mos. 7 days	+
124	34	3 yrs. 5 mos.	+

3. Plate cultures showing colonies having the characteristics mentioned under 2, but possessing definite agglutination reactions with polyvalent or type serum or both (Table 4).

TABLE 4.—COLONIES FROM JAIL CONTROLS POSSESSING DEFINITE AGGLUTINATION REACTIONS

Serial No.	Age (Years)	Time in Jail	Degree of Infection	No. of Colonies Exam.	Agglutination Reactions (Dilutions of 1:50 and 1:100)*	Type
1	53	1 yr. 4 mos.	±	1	Poly., ++; normal, ++; para, 0	Normal
20	21	1 mo. 6 days	±	2	Poly., ++; normal, 1:50, +; para, ++	Irregular para
21	34	1 mo. 29 days	++	1	Poly., ++; normal, ++; para, 0	Normal
22	29	11 days	+++	1	Poly., ++; normal, 1:50, +; para, ++	Irregular para
28	27	3 mos.	+	1	Poly., ++; normal, 0; para, 0	Irregular
50	23	1 mo. 27 days	±	1	Poly., ++; normal, ++; para, 0	Normal
82	20	17 days	±	1	Poly., ++; normal, ++; para, 0	Normal
84	46	7 days	±	2	Poly., ++; normal, ++; para, 0	Normal
88	55	1 mo. 9 days	+	2	Poly., ++; normal, ++; para, 0	Normal
89	34	1 mo. 6 days	+++	2	Poly., ++; normal, ++; para, 1:50, +	Irregular normal
102	39	19 days	±	1	Poly., ++; normal, 0; para, 0	Irregular
112	30	29 days	±	1	Poly., ++; normal, 0; para, ++	Para
117	20	1 mo. 14 days	++	1	Poly., ++; normal, 0; para, 0	Irregular
122	38	2 mos. 14 days	±	2	Poly., ++; normal, ++; para, 0	Normal
123	38	2 mos. 14 days	+	1	Poly., 0; normal, ++; para, 0	Normal
135	32	1 mo.	±	1	Poly., 0; normal, ++; para, 0	Normal
145	30	1 yr. 11 mos.	±	1	Poly., ++; normal, ++; para, 0	Normal
151	16	4 mos. 20 days	+	3	Poly., ++; normal, ++; para, 0	Normal

* ++ Indicates complete agglutination in a dilution of 1:100; +, incomplete agglutination in the dilution stated.

4. To the last mentioned may be added plate cultures yielding colonies indistinguishable from spinal strains but having no definite type reactions and showing a definite sedimentation along with a slight

agglutination with Flexner's serum, but not with normal horse or type serum. As they all reacted similarly, these cultures were placed in one group, as given in Table 5.

TABLE 5.—GROUP OF CULTURES SHOWING SEDIMENTATION AND SLIGHT AGGLUTINATION WITH FLEXNER'S SERUM

Serial No.	Age (Years)	Time in Jail	No. of Colonies Examined	Degree of Infection
41	25	24 days	1	±
106	29	1 mo. 28 days	1	±
114	45	1 mo. 1 day	1	±
131	39	6 days	1	±

Summarizing the results of the positive cultures, we find that there were:

Normal types (corresponding to Type II of the English classification)....	11
Para type (corresponding to Type I).....	1
Irregular normal type.....	1
Irregular para type.....	2
Irregular (no agglutination with normal or para only with polyvalent serum)	7
Inagglutinable types	5
Cultures impossible to agglutinate as no growth was obtained.....	5
Total	32

Therefore, notwithstanding the fact that no cases occurred in the jail, we find in the series of prisoners examined, that 24.6 per cent. harbored meningococcus-like organisms in the nasopharynx.

The age of the inmate apparently had no bearing on the carriage of the meningococcus.

The length of time of detention in the jail previous to the taking of the culture is summarized in Table 6.

TABLE 6.—TIME IN JAIL PREVIOUS TO MAKING CULTURES

Number of	Up to 1 Month	1 to 3 Months	3 to 6 Months	6 to 12 Months	After 1 Year
Negatives:	32	31	10	13	12
Positives:	9	18	3	0	2

It will be noted from Table 6 that most of the inmates showing positive cultures had been confined up to three months. The epidemic was four to five months in its course when the cultures were taken. The inmate who carried the para type—the type prevailing in the epidemic—was confined twenty-nine days. Two others, infected with irregular para types—also found in a very few patients—were confined eleven and thirty-six days previous to the culture. It appears, then, that the older prisoners, under the conditions of life in this

prison, apparently become to a great extent free from the meningococcus. It also appears that the few inmates who harbor the type prevailing in the epidemic have been recently confined.

With reference to the degree of infection, it is interesting to note that most of these carriers harbored only a few or occasional organisms. In 4 of the 32 carriers, however, they were numerous (++) , and in two the meningococcus was the predominating organism (+++). The only inmate who carried a para type — the prevailing type of the epidemic — was lightly infected.

In several instances, more than one colony of the same plate culture was examined for type. The results confirm the already established fact that the meningococci isolated from the same nasopharynx are usually of the same type.

Finally, an analysis of the types found shows that only one inmate yielded a para organism. On the other hand, 34.3 per cent. of the carriers yielded the normal type and the remainder (excluding 5 in whom no serologic tests could be made) or 50 per cent. of the carriers, harbored irregular or inagglutinable types.

In conclusion, the results of the swabbing of a number of inmates of the jail show that 24.6 per cent. were carriers of organisms indistinguishable from meningococci; that these carriers yielded types which, generally, were not found among the patients, namely, normal, irregular or inagglutinable organisms. Also, the percentage of carriers in the jail was higher than that demonstrated by others among the contacts with patients during the epidemic. Finally, among the 600 or more prisoners, no case of epidemic meningitis developed.

OTHER EPIDEMIOLOGIC FACTORS

In view of the fact that the following observations were made during an epidemic in a civil population, they are of interest for comparison with the experiences obtained in the Army and Navy.

(a). *The Influence of Age and Sex.* — From the local hospital records of 417 patients it will be noted that the ages of the patients ranged from 4 months to 59 years; the average age was 22.68 years. From the record of the Medical Officer of Health, based on the first 750 cases, mainly fatal, the great peak of the curve of age incidence is from infancy to 5 years; a lesser curve is seen at 17½ years.

The number of male cases at the local hospital was over twice that of the females; the official records show males to have been only slightly in excess of females. These figures when compared with the numbers of the sexes of the normal population, would be corrected so that the number of male cases is in excess of female only among the young adults.

Therefore, the susceptible elements of the population are the children, with no definite sex preponderance, and young adult males.

(b). *Influence of Meteorologic Conditions.*—The temperature, the mean as well as the wet-bulb (temperature of saturation), had a marked influence on the incidence of the disease. In general terms it may be stated that when there occurred a sudden drop of temperature, the number of cases increased, and when there was a rise in temperature, the incidence of epidemic meningitis declined. From a chart prepared by the Medical Officer of Health, one may formulate a table to show this relationship (Table 7).

TABLE 7.—FLUCTUATION OF NUMBER OF CASES WITH TEMPERATURE VARIATIONS

Date	Degree of Drop (Temp. of Saturation)	No. of Cases (In- crease Over Previous Low Level)	Time Elapsed Between Drop of Temp. and Increase of Cases
2/14-2/18	About 13° C.	11	4 days
2/27-3/ 2	About 11° C.	8	4 days
3/10-3/12	About 9° C.	4	2 days
3/25-3/27	About 12° C.	15	5 days
4/ 9-4/11	About 14° C.	5	5 days

On the other hand, the effect of a rise of temperature on the incidence of the disease can be formulated as in Table 8.

TABLE 8.—EFFECT OF RISE OF TEMPERATURE ON THE INCIDENCE OF THE DISEASE

Date	Degree of Rise (Temp. of Saturation)	No. of Cases (De- crease Over Previous Low Level for Week)	Time Elapsed Between Rise of Temp. and Decrease of Cases
2/18-2/27	About 20° C. (gradual rise)	8	8 days
3/15-3/24	About 17° C. (gradual rise)	4	8 days
3/31-4/ 9	About 13° C. (gradual rise)	4	4 days

Subsequently, as the temperature rose there was a corresponding decrease in the number of cases.

From the above it will be seen that as a rule about four days after a drop in temperature there was a great increase in the number of cases reported. The correspondence of this number with the number of days of the incubation period of epidemic meningitis is quite suggestive.

The influence of sunshine has also a relationship to the number of cases. For example, the period from February 28 to March 3 (four days) showed only 5½ hours of sunshine. Three days later, 23 cases were reported, the greatest number reported for a day with one exception. There was practically no sunshine for four days from March 26; on the fourth day after this period, 21 cases were reported, although there were only from 5 to 15 cases for the previous week. Thus, the lack of sunlight shows a relationship to the increase in the number of cases.

It is doubtful whether humidity or rainfall by themselves have any bearing on the number of cases. January and February were extremely dry months. Indeed, the rainfall was considerably below the average for several years. Yet February saw increasing numbers of cases, and March with a relatively small amount of rainfall, the greatest number. Similarly with the humidity; increasing humidity bore no relation to the number of patients.

(c). *Pre-epidemic Infections*.—It is a matter of common knowledge among the practitioners, although no official records are available, that many cases of sore throat were prevalent in the district during the period preceding the epidemic (November and December, 1917). The ailment was not severe, but at times it resembled influenza. Its distribution, however, was widespread.

On the other hand, there is no evidence of any increase in the incidence of measles or mumps.

(d). *Migration of the Population*.—The effect of emigration² from the district on the widespread dissemination of the disease is clearly shown. A few weeks after the outbreak cases were noted (and in most instances for the first time) in five cities along the trade routes north and south of the district. The cases numbered from a few to sixty, and in one instance nineteen out of twenty cases yielded a parameningococcus, the prevailing type.

The influence of immigration, on the other hand, on the continuation of an epidemic suggests itself. The entrance of a new, susceptible element of population from a noninfected district and its existence in close contact with the disease should increase the number of cases. Or a disturbance of the ratio of insusceptibles of the native population is created, offering new soil for an outbreak. The extent of immigration may be inferred from the records of 1916 (72,405) and 1917 (98,232).

(e). *The Habits of the Natives*.—Certain infringements of the rules of hygiene which may have a special relationship to the spread of the disease are continually practiced by the Chinese of this district. The most flagrant are in connection with the street restaurants. The edibles are exposed to the open air and served in dishes which are not cleansed between the servings, so that what is in one man's mouth may be directly conveyed to another's. The other infringements relate to the use of common towels and drinking cups; the drying and sorting of food on the highways which are covered with expectoration.

2. The activity of emigration may be judged from the records for 1916 and 1917, namely, 117,653 and 96,298, respectively.

(f). *The Overcrowding of the Population.*—As the epidemic was limited to a great degree to the overcrowded sections, it is important to describe this condition in detail.

Three causes operate to effect overcrowding. In the first place, there are too many houses on too small a space. Structures are in close proximity, separated from one another by narrow, chimney-like areaways. The lanes and areaways are so narrow, especially in proportion to the height of the houses, that not only ventilation but also light becomes deficient. The air is likewise damp almost all the time, from the wetness of the passageways.

In the second place, there are no arrangements for ventilation within the houses. For example, a house having a content of 5,818 cubic feet, has a window area of 51.8 square feet. One of the windows opens into a narrow street, the other into an oblong areaway of the diameter of a large steamship funnel. Besides, to avoid thieving or intrusion, the windows and doors are usually bolted, making the air very foul.

In the third place, there are too many inmates within a house. A floor of a dwelling is divided into boxlike compartments, called cubicles. There are from four to six cubicles to a floor. They are solidly partitioned off and the entrance curtained, so that no air whatever is admitted. This is the case as a rule, although exceptions may be found in the first or last cubicle. A typical cubicle on investigation revealed that its content is 336 cubic feet of unventilated air space. This cubicle is the dwelling of six persons. It is a frequent occurrence to find twenty persons existing on a floor space of 270 square feet.

The tendency of the Chinese to overcrowd is noted throughout the community. The market is crowded, so are the streets, the street cars, the lodging houses, native schools and matsheds.

Hence, there are too many houses on too small an area; there are no sanitary arrangements for light and air within the houses; there are too many persons living within the houses, and there is an innate gregariousness — all causing dense overcrowding.

(g). *Geographical Distribution of Cases.*—It is of interest to note that while it was of rare occurrence that more than one member of a family was afflicted, yet the greatest number of cases occurred in limited areas. Briefly, these areas comprised the most overcrowded sections. Indeed, in proportion to the same number of inhabitants, sparsely settled or less crowded areas yielded none, or an occasional case. Within the crowded district there are sections still more densely congested; the percentage of incidence to the population in the latter areas was three times that of the former.

EPIDEMIOLOGIC CONCLUSIONS AND DISCUSSION

The conditions prevailing in the district have been stated, and an attempt will be made to draw from them epidemiologic conclusions. The conditions usually prevailing during a pre-epidemic period occurred here as well, namely, an extremely cold winter combined with a large number of cases of pharyngitis, bronchial affections, and possibly influenza. In view of previous experience, these circumstances are favorable for the development of cases of epidemic meningitis, but they do not explain the great spread of the disease in the district, especially in certain sections.

(a). *The Influence of Overcrowding.*—The factor of greatest importance in the dissemination of the disease is the extensive overcrowding. The bases on which this conclusion rests are:

1. The meteorologic conditions.
2. The relative incidence of the disease in crowded and in uncrowded sections.
3. The bacteriologic evidence obtained from the patients.
4. The relation of the carrier.

It has been demonstrated above that *meteorological factors* have an important relationship to the dissemination of the disease: cold weather, especially in the absence of sunshine, resulted in an increase in the number of cases.

The effect of cold weather on the population is remarkable. As soon as it is felt, the natives abandon the habit of sleeping out in the open streets and highways, and literally swarm in the cubicles. These cubicles, as already stated, are boxlike compartments completely closed in and absolutely unventilated.

The mechanism of dissemination of the organism is more or less direct. It "consists in the ejection of the nasopharyngeal secretions into the surrounding atmosphere. This ejection does not take place during ordinary breathing, and little, as a rule, during quiet speaking. But in loud speaking and particularly in coughing, sneezing, hawking, and spitting, the secretions may be sprayed and scattered widely."³ Should one inmate harbor the meningococcus, it will be soon distributed over all the others of the dwelling. Thus, while the meningococcus is a very fragile organism and succumbs easily in external nature, in this condition of overcrowding and close contact induced by the cold weather, a general distribution is favored.

It is logical to assume that in a dark and damp atmosphere the viability of the organism is prolonged, favoring as well its spread from one to another.

3. Flexner, Simon: Mode of Infection, Means of Prevention and Specific Treatment of Epidemic Meningitis, J. A. M. A., 69:639, 1917.

The relative incidence of the disease in crowded and uncrowded sections adds further evidence. As shown in the foregoing, the disease took its greatest toll from the crowded districts. Among the foreign element an occasional case developed; among the Chinese it was common. Yet epidemic meningitis is not a disease peculiar to the Chinese.

On the other hand, in a neighboring city where there are four times as many Chinese, but not so densely settled, and where there is no cubicle system of dwelling, but the people live in ventilated rooms, not a single case developed among the natives.

The *bacteriologic evidence* obtained from patients is suggestive of the spread of the disease by close contact. Almost all (95 per cent.) the patients examined were infected with one type, the parameningococcus. As other types were found in the community, it is reasonable to assume (among other things) the rapid communicability of this type one to another — a result of the great density of the population.

The *relation of the carrier* in comparison with overcrowding was studied in the inmates of the jail. The results show that 24.6 per cent. of the 130 inmates examined were carriers of various types of meningococci. Yet at this institution not a single case developed. The important fact is that there are isolated cells there and no crowding.

Also among contacts, Europeans showed 9.8 per cent., while Chinese showed 6.7 per cent. of carriers. Yet the Chinese by far outnumbered the European cases.

This evidence leads to the conclusion that overcrowding is the important factor in the spread of the epidemic. At the same time, one must regard the carrier as a *sine qua non* as regards the source and the agent of transmission of the disease.

It appears, however, that the actual numbers of carriers present have only little epidemiologic significance. It is the type which is carried that is significant. Patients yield para types; the prisoners, although within the epidemic area but among whom no case develops, yield practically only normal, irregular, and inagglutinable types. The question of their relationship is still under investigation. However, it appears to favor the view recently stated by Flexner⁴ that in healthy carriers one type (the saprophytic), while in the epidemic cases another (the pathogenic), prevails.

(b). *Other Factors Contributing to the Continuance of the Epidemic.*—The epidemic having gained headway, it is possible that its continuance depended on the constant migration and the unhygienic habits of the natives: the many ways prevailing in the Chinese community of distributing nasopharyngeal secretions from one to another.

4. Flexner, Simon: Control of Meningitis, J. A. M. A., 71:638, 1918.

RECOMMENDATIONS FOR PREVENTION

The local conditions led to a formulation of the following means of prevention. The efficacy of these means cannot be judged until the next cold season will have passed. In outline form they are:

(a). The education of the Chinese in order to effect an active cooperation with the health and sanitary authorities.

(b). The prevention of overcrowding.

(c). The prevention of droplet infection by the instruction of the principles of personal hygiene and the employment of masks.

(d). The detection and treatment of contact carriers including the isolation of the "dangerous" carrier (one who harbors numerous meningococci, particularly of the same type as the patient).

(e). The isolation of the patient.

(f). Although still in an experimental stage, the use of preventive inoculation of an antimeningococcic vaccine.

CONCLUSIONS

In four of ten moribund cases of epidemic meningitis, the meningococcus was found circulating in the blood. It is difficult to interpret these findings with regard to the theory that blood invasion is primary or secondary, as in these cases the results were obtained antemortem. However, it emphasizes the need of intravenous combined with the intraspinal methods of treatment.

Serums having a low agglutinin content were therapeutically ineffective.

About 95 per cent. of the patients were infected with one type, the parameningococcus; the remainder with the irregular para type.

In a series of prisoners, who lived under hygienic conditions, 24.6 per cent. were found to be carriers. Of these, 50 per cent. yielded irregular or inagglutinable types and 34.3 per cent. the normal type, and only one person the para type. Although the jail is within the epidemic area, not a single case of meningitis developed therein.

These and other facts already stated have led to the conclusion that dense overcrowding of population and the presence of a pathogenic type of meningococcus, rather than the actual numbers of healthy carriers of various types of the organism, are the causes of the great spread of this epidemic.

BIOCHEMICAL STUDIES OF PNEUMONIC EXUDATES

WITH SPECIAL REFERENCE TO THE MECHANISM OF THE CRISIS IN
PNEUMONIA *

STUDIES IN PNEUMONIA. X

CHARLES WEISS, PH.D.

PHILADELPHIA

In a previous communication¹ we demonstrated the following properties of pneumonic lung exudates:

1. Salt solution extracts of human lungs in the stage of gray hepatization in pneumococcus lobar pneumonia are more toxic for experimental animals than similar extracts of normal lung tissue. The method of extraction influences the toxicity of both extracts.

2. Lethal doses of extracts of both pneumonic and normal lung tissue injected intravenously usually produce anaphylactic-like symptoms.

3. Sterile extracts of pneumonic lung tissue of dogs removed forty-eight hours after intrabronchial insufflation of virulent pneumococci are more toxic than similar extracts of consolidated lung following intrabronchial insufflation of sterile aleuronat in suspension and both of these are somewhat more toxic than extracts of equal weights of normal dog lung.

4. The toxicity of extracts of normal and pneumonic lung is decreased by heating, drying and filtration through porcelain filters.

5. Extracts of human pneumonic lungs in gray hepatization are hemolytic for guinea-pig cells, whereas similar extracts of normal human and dog lungs and of consolidated dog lungs following the intrabronchial insufflation of virulent pneumococci and sterile aleuronat, are generally nonhemolytic. The hemolytic activity of these extracts is neutralized by horse antipneumococcus serum as well as by normal rabbit serum; it is reduced by heating and drying and usually completely removed by porcelain filtration.

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*Part of a dissertation presented by the writer for the degree of Doctor of Philosophy, University of Pennsylvania, 1918.

*Aided by the Fels grant for research in pneumonia.

1. Weiss, C., Kolmer, J. A., and Steinfeld, E.: The Toxicity of Pneumonic Lungs, *J. Infect. Dis.* **22**:469, 1918.

6. Extracts of human pneumonic lung in gray hepatization inhibit the agglutinating activity of antipneumococcus serum.

The present investigations deal with further biologic and chemical analyses of the toxic substances in pneumonic exudates.

METHOD OF STUDY

The method of study consisted in anaphylactic sensitization and intoxication of guinea-pigs with various proteins derived from normal and pneumonic lungs, exudates, serums, etc. It has been recently shown by White and Avery² and particularly by C. L. A. Schmidt³ that the anaphylactic test is a very accurate one for the study of the biologic specificity of proteins. These anaphylactic tests were supplemented by studies of the comparative toxicity for rats and rabbits of the various proteins isolated. Their hemolytic activity was also determined. For the sake of accuracy all tests were done either in duplicate or in triplicate.

TABLE 1.—RESULTS OF ANAPHYLACTIC TESTS WITH HUMAN NORMAL AND PNEUMONIC EXUDATES

Weight of Guinea-Pig, Gm.	Sensitizing Substance	Intoxiating Substance	Results*
235	Pneumonic exudate	Pneumonic exudate	+++
254	Pneumonic exudate	Normal lung exudate	—
206	Normal lung exudate	Normal lung exudate	+++
222	Normal lung exudate	Pneumonic exudate	—

* In this and the following tables +++ = very severe anaphylactic shock, with death and typical necropsy findings; ++ = very severe anaphylactic shock with recovery; + = moderate shock with recovery; — = no reaction.

In our preliminary experiments we worked with whole phenolized exudates prepared according to the technic given in our first paper.¹ The tests were conducted as follows:

One series of guinea-pigs was sensitized by intraperitoneal injection of the exudate obtained from normal lung and another series with that of pneumonic lung. Fourteen days later half of each series were intoxicated by intravenous injections of normal and the other half of pneumonic lung exudate.

The reactions obtained in each series were clearly specific. Guinea-pigs sensitized with a dose of 0.2 c.c. (corresponding to 40 mg. of dried exudate) per kilogram reacted when injected intravenously

2. White, B., and Avery, O. T.: Some Immunity Reactions: The Biological Reactions of the Vegetable Proteins, III, J. Infect. Dis. **13**:103, 1913.

3. Schmidt, C. L. A.: Studies on the Formation and Antigenic Properties of Certain Compound Proteins, Univ. of California Pub. in Path. **2**:157, 1916.

with a similar dose of the corresponding substance. Control animals receiving this dose on primary intravenous or intraperitoneal injection showed no symptoms. The results are shown in Table 1.

After having thus demonstrated the existence of a specific sensitizing substance in the exudates of human pneumonic lungs in the stage of gray hepatization, we set out to determine its chemical and biologic nature: its specificity, its relation to pneumotoxin and pneumococcus protein, to the normal serum proteins, and the proteins of the lung tissue substance itself.

For this purpose anaphylactic tests were conducted according to the scheme shown in Table 2.

TABLE 2.—RESULTS OF ANAPHYLACTIC EXPERIMENTS WITH HUMAN PNEUMONIC EXUDATES *

Weight of Guinea-Pig, Gm.	Sensitizing Substance	Intoxicating Substance	Results
220	Pneumonic exudate	Emulsion of heat-killed pneumococci	—
203	Emulsion of dead pneumococci	Pneumonic exudate	—
470	Pneumonic exudate	Pneumotoxin	++
265	Pneumotoxin	Pneumotoxin	+++
240	Normal human serum	Serum of toxic pneumonic patient	+++
240	Normal human serum	Pneumonic exudate	++
203	Antipneumococcus horse serum	Pneumonic exudate	—

* Sensitizing doses were 0.2 c.c. per kilogram. Intoxicating doses were somewhat less and always much below the minimum lethal dose, as determined by control injections.

The following facts are evident from these experiments:

1. Pneumonic exudate contains normal serum proteins and pneumotoxin.
2. Pneumonic exudate contains neither undigested pneumococcus protein nor albumin derived from lung tissue which possesses sensitizing powers.

With the object of studying the chemical nature of the pneumonic exudate under more controlled conditions, we sensitized guinea-pigs with the serums and lung exudates of dogs removed forty-eight hours after intrabronchial insufflation of virulent Type I pneumococci after the method of Lamar and Meltzer,⁴ and also with similar material obtained from normal dogs. A protocol of these experiments is of dogs insufflated with virulent pneumococci. This observation is in given in Table 3.

The following points are to be observed:

4. Lamar, R. V., and Meltzer, S. J.: Experimental Pneumonia by Intra-bronchial Insufflation, J. Exper. M. 15:133, 1912.

1. Pneumotoxin is demonstrable in the lung exudate and serum accord with our previous findings with the use of an intracutaneous skin test.⁵

2. During the forty-eight hour interval between insufflation with virulent pneumococci and death of the animal by chloroform no specific sensitizing proteins (other than pneumotoxin) are developed in the exudate.

3. Pneumonic exudate contains *normal* serum proteins, leukocytes and blood fibrin.

TABLE 3.—RESULTS OF ANAPHYLACTIC EXPERIMENTS WITH MATERIAL OBTAINED FROM DOGS SUFFERING WITH EXPERIMENTAL LOBAR PNEUMONIA

Weight of Guinea-Pig, Gm.	Sensitizing Substance	Intoxicating Substance	Results
210	Normal lung exudate	Pneumonic lung exudate	++
205	Pneumonic lung exudate	Normal lung exudate	+++
225	Pneumonic lung exudate	Pneumonic lung exudate	+++
215	Pneumotoxin	Pneumonic lung exudate	+
215	Pneumotoxin	Serum pneumonic dog	++
265	Pneumotoxin	Pneumotoxin	+++
200	Pneumonic lung exudate	Serum normal dog	++
220	Pneumonic lung exudate	Serum pneumonic dog	+++
230	Normal dog leukocytes	Pneumonic lung exudate	++
260	Pneumonic lung exudate	Normal dog blood fibrin	+++
215	Normal dog blood fibrin	Pneumonic dog blood fibrin	+++
165	Serum pneumonic dog	Serum normal dog	+++

The lung exudate of dogs insufflated with virulent pneumococci is therefore similar to exudates obtained from cases of lobar pneumonia in man. It seems probable that the specific sensitizing protein present in the human gray hepatized lung is a product of the prolonged digestive action of the enzymes of the exudate on the normal serum albumin which is a constituent of the exudate. Müller's⁶ observation that the enzymes of the pneumonic exudate are foreign to the lung and our own finding (see following) that the albumin obtained from pneumonic exudates is, judging by the specific anaphylactic reaction and higher toxicity, more or less different from the albumin obtained from a normal human lung exudate, are in accord with this view. This problem requires further experimental study and will be discussed more fully later.

5. Weiss, C., and Kolmer, J. A.: A Skin Reaction to Pneumotoxin, *Proc. Soc. Exper. Biol. and M.* **15**:93, 1918; *J. Immunol.* **3**:395, 1918.

6. Müller, F.: Ueber die Chemischen Vorgänge bei Lösungen der Pneumonie, *Verhandl. d. Naturforsch. Gesellsch., Basle* **13**: 1912.

It was deemed advisable to confine our studies to human pneumonic exudates. Preliminary experiments showed that there probably exists no qualitative difference in the amino-acid content of exudates of normal lungs and pneumonic lungs in the stage of gray hepatization. All uniformly gave the biuret, Millon's xanthoproteic, Hopkins-Cole and Heller's test. We therefore prepared from these exudates albumins, globulins and albumoses, and studied their specificity by anaphylactic sensitization of guinea-pigs and their comparative toxicity on primary injection into white rats and rabbits.

Technic of Fractionating Exudates.—Human pneumonic lungs in the stage of gray hepatization and normal lungs (showing no involvement or only a slight degree of postmortem congestion of the posterior lobes) were obtained immediately after necropsy. The tissue was cut into small pieces, washed free from blood with running water, mixed with salt and strained through thick sterile cheesecloth. The thick viscid fluid thus obtained was centrifuged for one hour at very high speed in a powerful electric centrifuge and the clear supernatant fluid was used for analysis.

The globulins were precipitated by the method of Banzhaf.⁷ An equal volume of saturated ammonium sulphate solution was added and the precipitation was allowed to continue over night. The precipitate was centrifuged, washed with half saturated ammonium sulphate, taken up in distilled water and reprecipitated as before. It was again washed, dried at 20 C. by means of an electric fan, pressed between several layers of thick filter paper in a Buchner press, but not dialyzed. Dialyzation was deemed impracticable owing to the small amount of precipitate obtained. Control experiments showed that the retained ammonium sulphate in no way vitiated the results of the experiments. Chloroform and toluol were used throughout these analyses to prevent putrefaction.

The albumins were precipitated by complete saturation of the filtrate with crystals of ammonium sulphate ($\text{NH}_4)_2\text{SO}_4$). This precipitation was permitted to continue over night in the presence of 1 per cent. acetic acid. The precipitate was centrifuged, redissolved and reprecipitated in a manner similar to the technic described. It was finally pressed and dried.

The albumoses were prepared as follows: The acid albumins were dissolved in physiologic sodium chlorid solution containing 0.5 per cent sodium carbonate (Na_2CO_3). The solutions were now strongly acidified with acetic acid, boiled and coagulated. The filtrates were regarded as containing the albumoses.

Reference is made in Table 4 to albumins from pneumonic lung tissue; for the preparation of these the lungs were entirely freed from exudate by grinding first in a meat chopper, then with quartz sand in a mortar, and finally pressed in a Buchner press with a force of 350 kg. per square centimeter. The exudate-free tissue was now thoroughly and rapidly dried by means of an electric fan at room temperature. The dry powdered tissue was shaken with distilled water for several hours to dissolve the proteins. After removal of the sand and other insoluble material by centrifugalization, the globulins and albumins were precipitated, using the technic described.

7. Banzhaf, E. J., and Famulener, L. W.: The Proteins in the Serum of Goats Immunized Against Diphtheria, Collected Studies, Bureau of Laboratories, Dept. of Health, New York 8:208, 1914-1915.

Pneumotoxin (endocellular toxin of virulent Type I pneumococci) was prepared after the method of Cole⁸ as described by Cohen, Weiss and Kolmer.⁹

The various proteins mentioned, including pneumotoxin and pneumonic exudates, gave all the required color reactions for proteins. The exudate-free lung tissue did not react to the Hopkins-Cole test for tryptophan.

The protocols of anaphylactic experiments conducted with the various proteins thus prepared are given in Table 4.

TABLE 4.—RESULTS OF ANAPHYLACTIC EXPERIMENTS WITH GLOBULINS AND ALBUMINS FROM NORMAL AND PNEUMONIC LUNGS *

Weight of Guinea-Pig, Gm.	Sensitizing Substance	Intoxiating Substance	Results
215	Globulin normal exudate	Globulin pneumonic exudate	+++
245	Globulin pneumonic exudate	Globulin normal exudate	++
425	Albumin pneumonic exudate	Albumin normal exudate	—
380	Albumin normal exudate	Albumin pneumonic exudate	—
190	Albumin normal lung tissue	Albumin normal lung tissue	+++
201	Albumin normal lung tissue	Albumin pneumonic lung tissue	+++
181	Albumin pneumonic lung tissue	Albumin pneumonic lung tissue	+++
200	Albumin pneumonic lung tissue	Albumin normal lung tissue	++
224	Globulin pneumonic lung tissue	Emulsion dead pneumococci	—
225	Albumin pneumonic lung tissue	• Normal human active serum	+++
171	Egg albumin (Merek)	Albumin pneumonic lung tissue	—
235	Pneumonic exudate	Albumin pneumonic lung tissue	—
245	Pneumonic exudate	Albumin normal lung tissue	—

* Sensitizing dose was 0.1 gm. per kilogram in 1 per cent. solution in saline intraperitoneally. The intoxicating dose was somewhat less and always much below the minimum lethal dose, as determined by control injections.

The following points are to be observed:

1. The globulin fractions of human pneumonic and normal lung exudates are identical.

2. The albumin fraction of the pneumonic exudate possesses *marked* specificity and is related to the normal serum proteins.

3. Albumin from pneumonic lung tissue (freed from exudate) possesses no specificity and is also related to the normal serum proteins.

The validity of these conclusions was corroborated by the following observations on the comparative toxicity of the various lung proteins:

1. Globulins of both pneumonic and normal lung exudates are not toxic, producing no erythema or edema when injected intracutaneously into guinea-pigs in doses of 0.1 c.c. of a 1 per cent. solution in physi-

8. Cole, R.: *Pneumococcus Hemotoxin*, J. Exper. M. 20:346, 1914.

9. Cohen, S. S., Weiss, C., and Kolmer, J. A.: *On the Toxic Substances from Virulent Pneumococci*, J. Infect. Dis. 22:476, 1918.

ologic sodium chlorid solution, after the method of Wells and Hedenburg.¹⁰

2. Globulin of pneumonic lung (freed from exudate) is not toxic on intravenous injection into rabbits in doses of 5 mg. per kilogram (dissolved in physiologic sodium chlorid solution).

3. Albumins from normal and pneumonic lungs (freed from exudate) possess the same degree of toxicity for rats on intraperitoneal injection.

4. Albumin from exudate of pneumonic lung is far more toxic than similar albumin from exudate of normal lung, when injected intraperitoneally into white rats.

TABLE 5.—COMPARATIVE TOXICITY OF ALBUMINS FROM NORMAL AND PNEUMONIC LUNGS (FREED FROM EXUDATE) *

Normal Lung			Pneumonic Lung		
Weight of Rat, Gm.	Size of Dose, Gm. per Kg.	Result	Weight of Rat, Gm.	Size of Dose, Gm. per Kg.	Result
64	1.0	Dyspnea; convulsions; died, one hour	67	1.0	Dyspnea; convulsions; died, 10 minutes
57	0.6	Toxic symptoms; recovered, two hours	53	0.6	Sick; recovered, two hours
59	0.4	Slight symptoms; recovered	71	0.6	Slight symptoms; recovered

* Rats were injected intraperitoneally with 2 per cent. solutions of the albumins in normal salt.

5. Albumoses from exudate of pneumonic lung are exceedingly more toxic than similar albumoses from normal lung exudate.

In this connection a word must be said as to the specificity and marked toxicity of the albumins obtained from pneumonic exudates. It must be remembered that complete saturation with ammonium sulphate precipitates not only the albumins but also toxic albumoses and antitrypsin, as shown by Cathcart.¹¹ It is probably the digestive action of the trypsin (united with the antitrypsin) of the pneumonic exudate which is responsible for much of the toxicity and specificity of the albumins. The globulin fraction, as Cathcart showed, does not behave similarly, hence their nonspecificity and nontoxicity. The presence of the toxic albumoses does not vitiate our results, since they do not produce anaphylaxis, and we have made control studies of their comparative toxicity when free from albumins.

These results are shown in Tables 5 and 6.

10. Wells, H. G., and Hedenburg, O. F.: Toxicity of Carotin, *J. Biol. Chem.* 27:213, 1916.

11. Cathcart, E. P.: On the Antitryptic Action of Normal Serum, *J. Physiol.* 31:497, 1904.

That the albumose fraction of the pneumonic exudate is much more highly toxic than the albumose of normal lung exudate is seen also from the following experiment.

Two rabbits weighing 2,300 and 2,350 gm. were injected intrathoracically after the method of Auld¹² with doses of 0.02 gm. of normal and pneumonic albumose (in 1 per cent. solution, neutralized) per kilogram, respectively. Four hours later the rabbit receiving the pneumonic albumose showed a rise of temperature from 103.4 F. to 105.8 F., marked dyspnea and appeared toxic and morose. The other rabbit showed no effects. The "pneumonic" rabbit was killed and

TABLE 6.—COMPARATIVE TOXICITY OF ALBUMINS AND ALBUMOSES FROM NORMAL AND PNEUMONIC HUMAN LUNG EXUDATES *

Normal Exudate			Pneumonic Exudate		
Weight of Rat, Gm.	Size of Dose, Gm. per Kg.	Result	Weight of Rat, Gm.	Size of Dose, Gm. per Kg.	Result
1. Albumins					
132	1.0	Very mild toxic symptoms	128	1.0	Severe dyspnea; recovered, 2 hr.
145	0.8	Very mild toxic symptoms	137	0.8	Very severe dyspnea; recovered, 1 hour
2. Albumoses					
55	1.0	Mild dyspnea	55	1.0	Very severe convulsions; moribund; dyspnea; recovered
65	0.8	Moderately severe respiratory disturbances	73	0.8	Collapsed
77	0.6	No symptoms	82	0.6	Severe convulsions with death in 3 hr.†

* Rats were injected intraperitoneally with 1 per cent. solutions of neutralized substances in physiologic sodium chlorid solution.

† Histologic section of the lungs of this rat showed acute hyperemia.

necropsy held on the third day, and sections were made of the lungs and kidneys. The former show that the bronchi are unaffected. There is no exudate and no involvement of the bronchial walls. There is, however, a hyperemia with slight hemorrhagic exudation into the alveoli in scattered areas. There is no consolidation. The predominating change is the hemorrhagic extravasation into the alveoli in certain areas. Histologic sections of the kidneys of this rabbit show acute hyperemia, particularly of the glomerulus, accompanied by a slight degree of intratubular hemorrhage. There is also a cloudy swelling of the tubular cells. The picture is that of an early stage of a diffuse nephritis. There are also areas of tubular distention due to the plugging up of tubules.

12. Auld, A. G.: Selected Researches in Pathology, 1901, Ch. 2 and 3. J. and A. Churchill, London.

It was of interest, in connection with our theory as to the rôle of the albumoses in the mechanism of the crisis in pneumonia (discussed later) to determine whether or not a tolerance or immunity to pneumonic albumose could be produced experimentally in animals. For this purpose each of the rats of Table 6 that had recovered after the injection of pneumonic albumose was reinjected intraperitoneally with a dose as large as the first. The rats showed only very mild reactions and none of the toxic symptoms that followed the first dose.

Additional studies were conducted on both normal and pneumonic lungs. Only brief reference can be made to these at this time.

Dried pneumonic lungs on extraction with ether in a Soxhlet apparatus yielded large amounts of lipoidal, nontoxic material. These lipoids when added to a suspension of guinea-pig erythrocytes were deposited on the surfaces of the latter, producing what appeared macroscopically as a cream-colored emulsion. Microscopically, the cells appeared to be undergoing poikilocytosis, but no hemolysis was evident after prolonged incubation. This phenomenon was also obtained with the use of pure lipid antigen used in the Wassermann reaction for syphilis. On fractionating the lung lipoids into an acetone-soluble and acetone-insoluble fraction, the former was found to be hemolytic, the latter not. Neither fraction, however, produced the poikilocytic phenomenon described. In view of the observation that removal of this lipoidal substance from pneumonic lung renders it more hemolytic, we conclude that its production in the exudate is in response to the injurious action of the hemolytic pneumotoxin. This is in accord with the findings of Cole,⁸ that lipoids such as cholesterol and lecithin inhibit hemolysis of erythrocytes by pneumotoxin, and the observations of Bogomolez¹³ that excess amounts of lipoids are formed in response to infection by toxin-producing organisms. The lipemia, acidosis and defective glycolysis observed in pneumonia, as well as the decrease in amount of lipase in pneumonic lungs, mentioned by Wells,¹⁴ can thus be traced to the influence of pneumotoxin.

Of the various protein fractions isolated and referred to in the foregoing, none were found to be hemolytic, except the pneumotoxin. The whole pneumonic exudate, as has already been stated, was always hemolytic to a far greater degree than normal exudate—even after one year's storage in a dried state. Solution of the protein fractions in bile, using the technic described for the preparation of pneumotoxin,⁹ did not yield hemolytic substances. The hemolytic activity of pneumonic exudates is therefore due to the presence of pneumotoxin as

13. Bogomolez: *Ztschr. f. Immunitätsforsch.* 8:35, 1910.

14. Wells, H. G.: *Chemical Pathology*, Ed. 3, W. B. Saunders Company, Philadelphia, 1918, pp. 413, 560, 78.

well as of various fatty acids, lactic acid and other products of autolysis observed by Lamar.¹⁵

Using the various protein substances referred to in this paper (excepting pneumotoxin) as antigen, no precipitin reaction was obtained on addition of various serologic types of antipneumococcus horse serum.

No pentose such as observed by Burnett¹⁶ in tissue of rat carcinoma was detected in our preparations.¹⁷ We concluded from all these experiments that other than pneumotoxin (the endocellular toxic protein liberated on dissolution of pneumococci) and the toxic albumose which is the result of the partial digestion of serum albumin during autolysis, no specific toxic proteins are formed during the course of an attack of lobar pneumonia in man.

DISCUSSION

The occurrence of toxic albumoses in pneumonic lungs, in the urine of patients suffering with lobar pneumonia, as well as in the tissues of rabbits having experimental pneumonic septicemia, was demonstrated by Simon,¹⁸ Matthew,¹⁹ Auld¹² and others many years ago. We pointed out their bearing on the mechanism of the crisis in pneumonia in earlier communications (Footnotes 9 and 20). While largely a matter of conjecture, this theory is of sufficient interest to warrant elaboration in the light of the data presented in this paper.

We regard the formation of the pneumonic exudate *in part* due to an increased permeability of the endothelial cells of the lungs for various *normal* serum albumins, globulins, fibrinogen and enzymes, resulting from the injurious action exerted by the pneumotoxin on their cement substance. The toxin is also assumed to act as a lymphagogue.

Other factors which, according to the recent studies of Jacques Loeb, M. Fisher and others,²¹ are active in the production of inflammatory edemas, play their usual rôle. Prominent are the impediment

15. Lamar, R. V.: Chemo-Immunological Studies in Localized Infections, J. Exper. M. **13**:1, 1911.

16. Burnett, T. C.: Note on a Toxic Nucleoprotein Obtained from Rat Carcinoma, Proc. Soc. Exper. Biol. and M. **14**:63, 1916.

17. The nucleoprotein fraction of pneumonic lung exudate, which was isolated but not fully studied because of the scarcity of guinea-pigs, also reacted negatively to the orcein test.

18. Simon, O.: Untersuchungen über die Lösungsvorgänge der croupösen Pneumonie, Deutsch. Arch. f. klin. Med. **70**: Parts 5 and 6, 1901.

19. Matthes, M.: Arch. f. exper. Path. u. Pharmacol. **36**:437, 1895.

20. Weiss, C.: The Properties of Pneumotoxin and Its Probable Rôle in the Pathology of Lobar Pneumonia, J. M. Res. **39**:103, 1918.

21. Epstein, A. A.: Concerning the Causation of Edema in Chronic Parenchymatous Nephritis, Am. J. M. Sc. **154**:638, 1917.

of lymph outflow caused by the plugging up of the lymphatic channels by clots and leukocytes, increased osmotic pressure and increased hydrophilic properties of the cells due to the action of lactic, formic and fatty acids, enzymes and other products of bacterial (pneumococcic) and cellular metabolism.

The exudate, therefore, is formed from *normal* constituents of the circulating body fluids which have been transferred to and have accumulated in the alveolar spaces. This migration has at least two distinct effects. First, it depletes the blood of its content of serum proteins, which normally has a tendency to be constant, thus producing a diminution in osmotic pressure which is compensated for by a retention of chlorids.²² Second, it brings to the lung a large excess of material which is foreign to it and which, therefore, would be subject to an *accelerated catabolism* (autolysis) in accordance with the law of mass action, in order to keep the blood proteins constant, to rid the lung of foreign proteins and to restore the physicochemical equilibrium of the body fluids.

We now assume that while the pneumococci proliferating in the body fluids may activate the enzymes that accomplish the autolysis of the fibrin, leukocytes, etc., in the lung,²³ their *toxins* tend to inhibit this autolysis with the production of only partly digested products: albumoses and peptones, such as demonstrated in the foregoing. These toxic products are pyrogenic, as pointed out by Jobling.²⁴ They act as lymphagogues, aid in further inhibition of autolysis and increase the coagulation time of the blood, as shown by Dochez.²⁵ Thus we account for what Riesman²⁶ has called the "metabolic toxemia" of pneumonia.²⁷ Moreover, the serum of the inflammatory exudate which is known to contain albumoses and peptones was found by Opie²⁸ to retard the action of the autolytic enzymes of the leukocytes. Weiss, Kolmer and Steinfield¹ also demonstrated the presence in pneumonic exudates

22. Peabody, F. W.: Studies of the Inorganic Metabolism in Pneumonia, J. Exper. M. **17**:71, 1913.

23. A. E. Taylor (Digestion and Metabolism, Lea and Febiger, Philadelphia, 1912, p. 138) points out that bacterial extracts and tissue juices activate proferments, such as pepsinogen.

24. Jobling, J. W., Petersen, W., and Eggstein, A. A.: Serum Ferments and Antiferments During Pneumonia, J. Exper. M. **22**:568, 1915.

25. Dochez, A. R.: Coagulation Time of the Blood in Lobar Pneumonia, J. Exper. M. **16**:693, 1912.

26. Riesman, D.: The Cellular Factor in Infectious Diseases, Tr. College Phys., Philadelphia **36**:271, 1914.

27. We have discussed the cause of the initial toxemia in another communication (Footnote 20).

28. Opie, E. L.: Enzymes and Anti-Enzymes in Inflammatory Exudates, J. Exper. M. **7**:316, 1905.

of substances that hinder the various defensive immunologic reactions of the body fluids.

Simultaneous with the production of the toxic substances thus far alluded to, we have the liberation of various specific antibodies²⁹ and of bactericidal and phagocytic substances.³⁰ The demonstration of these in vitro, before the crisis, is difficult and often impossible owing to the presence of excess amounts of antigen (pneumotoxin and albumose), as suggested by the work of Weil.³¹ With the production of excess amounts of immune bodies and *particularly of a tolerance or immunity to the toxic albumoses*, the deleterious and autolysis-inhibiting influences are removed.

It is also probable that the continuous action of the toxins, aside from antibody production, changes their primary inhibitory effect on autolysis into an accelerating one. This is suggested by the work of Hess and Saxl.³² This accelerated autolysis in turn hastens antibody production, as pointed out by Blum.³³ The products of autolysis are now completely digested proteins in the amino-acid stage which are nontoxic and easily absorbed and eliminated.

The equilibrium of the system described is governed by the laws of mass action as suggested by Taylor³⁴ and more recently by the work of Bayne-Jones.³⁴ Hence the change from febrile toxemia to the afebrile atoxic state is necessarily an abrupt one — crisis. The period is accompanied by the sudden drop in temperature, relief to toxemic symptoms, a decrease in amount of proteoses in the serum, return to normal coagulation time, and normal protein content of the blood.

The autolysis is probably accomplished by the proteolytic enzymes of the leukocytes. Hartman³⁵ suggests that the fibrin requires specific antibodies for its removal, but we are inclined to agree with Simon¹⁸ who concludes after thorough chemical investigations that the leuko-

29. Clough, P. W.: The Development of Antibodies in the Serum of Patients Recovering from Acute Lobar Pneumonia, *Bull. Johns Hopkins Hosp.* 24:205, 1913.

30. Winternitz, M. C., and Kline, B. S.: Studies on Experimental Pneumonia in Rabbits, IX, *J. Exper. M.* 21:320, 1915.

31. Weil, R., and Torrey, J. C.: Immunological Studies in Pneumonia, *J. Exper. M.* 23:1, 1916.

32. Hess, L., and Saxl, P.: Einfluss der Toxine auf den Eiweissabbau der Zelle, *Wien. klin. Wchnschr.* 21:248, 1908. *Ibid.*, Experimente an autolysierende Organe, p. 486.

33. Blum, L.: Ueber die Antitoxinbildung bei Autolyse, *Beitr. z. chem. Physiol. u. Path.* 5:142, 1904.

34. Bayne-Jones, S.: Equilibria in Precipitin Reactions, *J. Exper. M.* 25:836, 1917.

35. Hartman, C. C.: The Antigenic Properties of Fibrin (Exudate) to Serum, *J. Infect. Dis.* 13:69, 1913. The Antigenic Properties of the Constituents of Pneumonic Exudate, *Ibid.* 13:499, 1913.

cytic enzymes will digest the fibrin as well as the other constituents of the exudate. Ascoli³⁶ is of the opinion that isolysins are formed to remove the cellular constituents. He demonstrated such isolysins after the crisis.

That the pneumotoxin exerts no influence on the lung tissue itself and that the latter plays no part in the formation of the exudate is well known, as mentioned by Wells.¹⁴ Our own observations on the identity of the albumins of normal and pneumonic (exudate-free) lungs substantiates this.

CONCLUSIONS

Biochemical studies of pneumonic exudates obtained from human lungs in the stage of gray hepatization were conducted by the method of anaphylactic sensitization and intoxication of guinea-pigs with various proteins derived from normal and pneumonic lungs, exudates, serums, etc. The following observations were made:

1. Pneumonic exudates contain *at least two* toxic proteins: (1) a specific sensitizing protein apparently identical with the pneumotoxin which is liberated on the dissolution of virulent pneumococci, and (2) an extremely toxic, pyrogenic albumose.
2. There are also present normal serum proteins: serum albumin and serum globulin, leukocytes and fibrin.
3. Neither undigested pneumococcic protein nor albumin derived from the lung tissue, possessing sensitizing powers, are demonstrable.
4. The globulin fraction of human pneumonic exudate is nontoxic and identical with similar normal globulin.
5. The albumin fraction of pneumonic exudate is toxic and possesses marked specificity. This is ascribed to the digestive action of the enzymes of the exudate.
6. The albumose fraction is far more toxic. Dyspnea, convulsions and death follow the intraperitoneal injection into white rats of doses of 1 gm. per kilogram. Intrathoracic injection into rabbits of doses of 0.02 gm. per kilogram produces a rise in temperature, dyspnea, a hemorrhagic extravasation into the alveoli; of the lung and an acute diffuse nephritis. On repeated intraperitoneal injections of this albumose into rats, a tolerance to it can be established.
7. Large amounts of ether-soluble, nontoxic, hemolysis-inhibiting substances were extracted from pneumonic lungs. These are assumed to have the power of neutralizing the hemolytic activity of the pneumotoxin *in vivo*.
8. The formation of the exudate in pneumonia is considered to be *in part* due to an increased permeability of the endothelial cells of

36. Ascoli, M.: Isoagglutinine und Isolysine in menschlicher Blutsera, München. med. Wchnschr. 48:1239, 1901.

the lung for various *normal* serum albumins, globulins, fibrinogen and enzymes as the result of the injury exerted by the pneumotoxin on their cement substance. The toxin is also regarded as a lymphagogue. It hinders the autolysis of the exudate and the favorable action of antipneumococcus immune bodies and thus produces toxic autolysis-inhibiting, pyrogenic albumoses. With the development of excess amounts of specific antibodies, of bactericidal and phagocytic substances, and of a tolerance to the toxic albumoses, the deleterious influences of the toxins and albumoses are neutralized. Autolysis of the exudate is now unhindered and the products are nontoxic amino-acids. The equilibrium of this system being governed by the laws of mass action, the change from febrile toxemia to the afebrile, atoxic state is necessarily an abrupt one — *crisis*.

The writer wishes to express his indebtedness to Dr. John A. Kolmer, Dr. S. Solis-Cohen, Dr. B. M. Hendrix and Dr. A. E. Taylor for suggestions and criticisms given throughout the course of the work.

CORRECTION

Attention is called to errors in the legends of the charts illustrating the article in the February, 1919, number (p. 235) by A. O. Gettler and R. Oppenheimer on "Differentiation of Nephropathies, Cardiopathies and Allied Conditions by the Determination of Physical Constants." The legend of Chart 1 should read "Ash" instead of "Refractive index;" Chart 2 should be "Freezing point" instead of "Solids"; Chart 4 should be "Solids" instead of "Freezing Point"; Chart 5 should be "Refractive index" instead of "Ash." We regret that these errors occurred. Corrections have been made in the authors' reprints.

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EXTRAMENINGEAL MENINGOCOCCUS INFECTIONS

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The meningeal picture resulting from meningococcus infection has so fixed the attention of clinicians and pathologists that the possibilities of extrameningeal infection by the organism have had scant notice. This has resulted in a general failure to recognize the fundamental nature of the disease as a meningococcus septicemia, which has in turn had important consequences in the fields of diagnosis and treatment.

The reason for this is not obscure. The premeningitic stage of the disease, which, up to the present, has been called epidemic cerebrospinal meningitis, is ordinarily not impressive enough to be of serious concern to the family physician, and is rarely, if ever, seen by the hospital physician or the consultant. Meningococcus infections apart from meningitis are practically unrecognized in civil life. The local meningeal involvement and the symptoms arising therefrom have been the criteria of diagnosis. To this the skill and care required to cause the organism to grow in artificial mediums is contributory.

In the receiving ward of a large military hospital acute disease is observed in its incipency. The very hour the recruit in a well regulated camp is incapacitated from his severe routine, he is rushed to the base hospital where a specially trained staff awaits him. Under such conditions 315 cases of meningococcus infection were studied at Camp Jackson. In approximately 40 per cent. the diagnosis was made before meningitis developed. In 5 per cent. meningitis never developed at all. With few exceptions the earliest evidences of meningitis were preceded by symptoms of a general infection lasting from a few hours to several days, in exceptional instances, weeks. This initial stage of sepsis was repeatedly proved by blood culture, by clinical studies and necropsies. It has been sufficiently dwelt on in previous reports.¹ It is not our opinion, as one writer² has construed

1. Herrick, W. W.: The Epidemic of Meningitis at Camp Jackson, J. A. M. A. **70**:227 (Jan. 26) 1918. The Intravenous Serum Treatment of Epidemic Cerebrospinal Meningitis, Arch. Int. Med. **21**:54 (April) 1918. Early Diagnosis and Intravenous Serum Treatment of Epidemic Cerebrospinal Meningitis, J. A. M. A. **71**:612 (Aug. 24) 1918.

2. Neal, Josephine: Epidemic Meningitis, Med. Clin. North Am. **2**:223, 1918.

these reports, that epidemic cerebrospinal meningitis is a sepsis throughout its entire course. It is a blood stream invasion, a sepsis, at first, for a period averaging forty-eight hours, often more, at times less. Later there is the local process, usually in the meninges, not infrequently elsewhere.

Being revolutionary, this conception of the disease demands repeated emphasis. This emphasis is imperative because on it is based that modified therapy which, in proper hands, has mitigated the severity of the disease and greatly reduced the mortality—the intravenous serum treatment.

To emphasize the importance of the extrameningeal rôle of the meningococcus, both in the early stages of ordinary epidemic meningitis and in other less frequent conditions, the following cases are cited as types:

CASE 1.—*Meningococcus Sepsis without Meningitis.* The patient, B. A., a private, 21 years old, was admitted to the hospital, Sept. 29, 1918, with a typical mild influenza. The temperature was 101 F., and there was moderate bronchitis, with headache, joint pain, coryza and cough. The temperature became normal October 3 and remained so. October 7, at 7:10 a. m., the emergency officer noted that the patient had a chill in the early part of the night, with pain in the chest which made him groan aloud. Perspiration covered the entire body. The pulse was weak and frequent; the temperature subnormal. There were signs of broncho-pneumonia at the bases of both lungs.

By 10 a. m. a petechial rash appeared. The spots rapidly increased in size and number, extending over the trunk, arms, face and conjunctivae. The patient quickly sank into coma. The general condition was very poor and the temperature was constantly subnormal. There were no specific signs of meningitis. The spinal fluid was water-clear, contained no globulin, showed sugar and 12 cells per cubic millimeter, but neither pus cells nor organisms. A note at that time recorded the opinion that the condition was meningococcus septicemia; prognosis, hopeless.

Despite this situation a trial of intravenous treatment was made and after the usual desensitization and administration of morphin and atropin the patient received 100 c.c. of antimeningococcus serum by vein. The patient made no response and died at 11:30 a. m., one-half hour after admission to the meningitis ward and only six or eight hours after the initial chill. Cultures from the heart blood and from the spinal fluid taken immediately on death showed meningococci. At death the body was a mass of purpuric blotches.

The body was embalmed shortly after death. The brain was removed by Paul Wegeforth, Captain, M. C., U. S. Army, on the following day. It was well fixed by the embalming fluid and showed no gross lesion. The remaining part of the body was not examined.

Microscopic Examination.—This was made by W. H. Norton, Captain, M. C., U. S. Army, Necropsy 18A137. Sections of the floor of the fourth ventricle, the left temporal lobe, the left frontal lobe, the wall of the lateral ventricle, the wall of the posterior horn of the left lateral ventricle, the left occipital lobe, the cerebellum and choroid plexus were all normal. There was no congestion, cellular increase or exudate.

Diagnosis.—Meningococcus sepsis.

CASE 2.—*Meningococcus Sepsis.* The patient, a private, aged 21, was admitted to the X section of the base hospital late in the evening of Oct. 1, 1918, complaining of sore throat, general pains and weakness, all of which

had begun on the previous day. At 5:30 a. m., October 2, he complained of headache, increased weakness, pains in the back, legs and joints and sore throat. There was a petechial rash over the trunk, arms, legs and face. There were no definite meningeal signs or symptoms. At 7 p. m., October 2, he was apathetic, yet restless and was complaining of severe pain in all joints. His color was a combination of pallor and cyanosis, with a special cyanosis of the ears. The mouth was dry and coated. The heart and lungs showed nothing significant. The spleen was felt 1 inch below the costal margin. The neck was not stiff. There was tenderness and pain on manipulation of all joints with marked cutaneous hyperesthesia. There was no redness or swelling of the joints. The trunk, extremities, face and conjunctivae were covered with petechial spots, some three-fourths inch in diameter.

He was transferred to the meningitis ward as a case of meningococcus sepsis. All the deep reflexes were abolished. The joints were tender and painful on movement. General cutaneous hyperesthesia continued.

The patient died at 11:30 a. m., October 3. He had a subnormal temperature and an imperceptible pulse just before death. The blood cultures taken October 2 showed gram-negative diplococci giving the agglutination tests tabulated. For these I am indebted to Major Marshall A. Barber, S. C., U. S. Army, chief of the laboratory.

	Dilution				
	1:50	1:100	1:200	1:400	1:800
Rockefeller Institute antimeningococcus serum..	++	++	++	+	+
New York City Health Department serum.....	++	++	+		
Mulford.....	+	+			
Lederle.....	++	++	+	+	
Type 1 serum.....	±	+	Salt solution, negative Horse serum 1:50, negative		
Type 4 serum.....	++				
Type 10 serum.....	+				
Type 30 serum.....	±				
Type 60 serum.....	—				

Necropsy (18A136).—Necropsy performed at 9:30 a. m., Oct. 4, 1918, by P. Wegeforth, Captain, M. C. Private H. W. The body, seen just after death at 11:35 a. m., October 3, was that of a well developed man measuring 5 feet 8 inches. The skin of cheeks, eyelids, both arms, legs, body and shoulders was covered with large subcutaneous hemorrhages varying in size from a pinhead to a split pea. The petechiae on the upper arm were the most striking, and the largest. The outlines were irregular and presented no uniformity. Petechiae were present on the soft palate and both conjunctivae.

Head: The calvarium was easily removed and presented no abnormalities. The dura was normal in appearance, stripped easily from the bone and was lifted readily from the arachnoid. No petechiae were noted anywhere in the dura. The arachnoid was torn in places, but otherwise did not appear abnormal and no exudate could be noted beneath it, either over the hemisphere or base. The meningeal vessels over both hemispheres were apparently hyperemic in a slight degree, a condition which was not present over the base. No petechiae could be found on the leptomeninges. Sagittal section was made through the corpus callosum and the right lateral and third ventricles entered carefully. A very small amount of fluid was found in each, from which smears were made. The lateral ventricles appeared normal. The choroid plexus appeared normal.

Lungs: No fluid was present in either pleural cavity. The pleura over the bases of both lungs contained numerous petechiae of varying sizes, none larger than a split pea. Only a few scattered petechiae could be seen in the parietal layer, and they were located at the base. The organs themselves were normal. The bronchial lymph nodes were not enlarged.

Heart: The pericardium contained no excess of fluid. Within the membrane numerous petechiae were to be seen, especially in the visceral layer in the neighborhood of the apex and along each side of the coronary arteries. The parietal layer contained a few hemorrhages, but the number was small in comparison with those on the heart. The heart was normal in size. The endocardium and valves were normal, and no petechiae could be found in the cavity walls. The aorta was free of plaques.

Liver: Organ normal in appearance; no petechiae on its surface. On section the tissue had a slight yellowish cast in places.

Kidneys: Normal in size and appearance. On section no gross lesions were found. The pelves and ureters were normal; no petechiae in the capsules.

Pancreas: Normal.

Stomach and Intestines: No lesions found; no petechiae anywhere in peritoneum of intestines, mesentery or omentum.

Bladder: Wall in good condition; no petechiae noted in either external surface or in epithelium.

Prostate: Small, firm and on section showed no abnormality.

Bacteriology.—Blood Culture: Gram negative diplococcus with positive titer for meningococcus.

Ventricular Fluids: Postmortem smear negative for organisms.

Diagnosis.—Meningococcus bacteraemia with hemorrhage into skin, throat, conjunctivae, pleura and pericardium.

Microscopic Examination.—By W. H. Norton, Captain, M. C., U. S. Army.

Lung: The alveolar walls are congested with erythrocytes and serum; the blood vessels dilated.

Heart: The heart muscle is normal. The pericardium is thickened by a surface coat of serum and fibrin and slightly raised by large collections of erythrocytes.

Liver: The liver cells are greatly shrunken, vacuolated and contain some brownish pigment. The interspaces throughout the lobules are dilated, principally by serum and fibrin. The process is more marked around the central veins.

Kidneys: The glomeruli are distended with blood, likewise the vessels. The tubular epithelium is broken up, and in many places all the nuclei have disappeared. There is considerable serum, fibrin and some infiltration with round cells between the tubules.

The spleen shows marked congestion, there being some phagocytic cells filled with pigment.

Prostate normal.

Central Nervous System: The lateral wall of the right lateral ventricle is normal. The floor of the fourth ventricle shows marked dilatation of the blood vessels with some serohemorrhagic exudate over the pia mater. There are a few round cells, but no polymorphonuclears.

At the base of the temporal lobe there is some hemorrhage and round cell infiltration between the pia and arachnoid.

The mesial surface of the parietal lobe shows hemorrhage and cellular infiltration of the pia and subarachnoid coats. While mostly mononuclears, there is here and there a polynuclear leukocyte. A like condition obtains over the cerebellum.

The choroid plexus shows extreme dilatation of the capillaries with small cysts filled with serous exudate, congestion and infiltration with leukocytes both mononuclear and polynuclear.

No collections of polymorphonuclear leukocytes are found on any of the surfaces examined.

Diagnosis: (1) acute serous meningitis; (2) congestion of the lung, liver, spleen and kidneys; (3) parenchymatous degeneration of liver and kidneys; (4) acute pericarditis.

CASE 3.—*Subacute Meningococcus Sepsis without Meningitis but with Other Local Symptoms.* The most striking case of this type was that of the head nurse in the meningitis ward. She was a very intelligent, vigorous and active woman of 28, who was particularly careful about infection, constantly wearing a mask while on duty and spraying two or three times a day with a solution of dichloramin-T or other antiseptics. In fact the thoroughness with which this nurse carried out all possible precautions was a subject of remark among her associates.

Jan. 16, 1918, there was an attack of tonsillitis with slight fever, headache and pain over the region of the right maxillary sinus. She gave up her ward duty and spent most of the following week in bed. About Jan. 23, 1918, there was found to be a sinusitis which was treated locally. Two days later an acute polyarthritis began. This involved hips, knees, ankles, elbows and wrists in rapid succession with moderate pain, stiffness, tenderness and slight swelling. The local symptoms, rather than the systemic disturbance forced the patient to remain in bed. After one week there was a slight improvement and the patient returned to duty, where she remained for several days, annoyed only by stiffness and soreness in the joints. About February 11, after being on duty seven days, an operation was performed on the maxillary and ethmoid sinuses which were drained with a trocar. No culture was made from these sinuses. Forty-eight hours after this surgical experience, there was a recurrence of the arthritis with severe local and general symptoms. There was a rapid loss of weight, recurring chills and irregular temperature and a general picture suggesting a septic arthritis. The patient rapidly became anemic, extremely weak, had moderate headache and exhibited a maculopapular eruption, not unlike that of typhoid fever. Full doses of sodium salicylate were given without effect.

A blood culture made February 16 by Major F. W. Baeslack, was positive for meningococci. At this time the temperature was ranging to 101 F., the pulse rate averaged 120 and the respirations from 24 to 30. There was no rigidity of the neck, no Kernig's sign, no headache or nausea, nothing suggesting meningeal irritation. February 16, 55 c.c. of antimeningococcus serum were given by vein. This was followed by a chill, but no other reaction. February 17, the temperature was 100. The only complaint was of painful joints. Sixty c.c. of serum were given by vein. On the 19th an intravenous injection of 70 c.c. was given. February 19 a general improvement was noted. Previously apathetic and distressed, she was now bright and resting very comfortably. The arthritis had lessened. February 20, 160 c.c. of serum were given intravenously. On this date the temperature was 102.4. February 21, there was a marked serum rash which lasted about five days. Blood culture made February 20 was negative. Convalescence was satisfactory, though somewhat prolonged by rather poor response to exercise on the part of the heart and a rapid heart rate. She returned to duty about April 1 and has since performed very active service in the hospital laboratory with no sequel whatever.

Lumbar puncture was not done because there was not the slightest clinical evidence of meningeal involvement, a possibility to which those in charge were naturally alert.

The notable change in the condition of the patient under specific serum therapy is important. From a very serious, progressive septic polyarthritis with advancing anemia, prostration and other attendant evidences of toxemia, within forty-eight hours the patient's condition changed, and in four days she seemed out of danger and made a recovery marred only by severe serum sickness.

Unfortunately, no culture was made from the accessory nasal sinuses at the time these were drained, nor were any nasopharyngeal cultures made except the routine three cultures just before discharge. These were negative.

CASE 4.—*Meningitis Tarda with Prolonged Stage of Meningococcus Sepsis. Meningitis a Late Development.* The patient, L. S., aged 24, a private, was admitted to the base hospital, Feb. 21, 1918. For the previous two or three weeks he had been troubled with frontal headache, at times so severe that he "could not see." Just previous to admission there had been chill and vomiting. On admission the temperature was 100 F., the pulse 62. He did not appear very ill. The tonsils were enlarged, ragged, but without exudate. There was a papular rash on the body.

The picture was so suggestive of an early meningitis that a lumbar puncture was done shortly after admission, Feb. 21, and 10 c.c. of perfectly clear fluid were removed. There was no increase in cells, no globulin and no bacteria.

February 26 there was a chill followed by fever and headache. The heart was negative. On the extremities and back there were a few tender, reddish spots, varying in size up to 1 inch in diameter and having the general appearance of an erythema multiforme. The patient was transferred to the rheumatism ward and given salicylates, which were without effect. March 9 there was a renewal of the headache. With this was no rigidity of the neck or abnormality of the reflexes. The left tonsil was ulcerated. The temperature was 103.6; the pulse, 98. On April 4, 1918, the temperature, after remaining normal two days, rose to 102.4. The throat and lungs were negative. Examination for malaria organisms was repeatedly negative. April 13 he complained of pain in the knees. These joints were slightly swollen, tender and hot.

During all this prolonged hospital stay, the patient was not very ill. It was difficult to keep him in bed and during the remissions in his symptoms he would get up and walk about the ward, often against orders. There was very little prostration, but he was dull, apathetic and his nutrition suffered. The temperature was extremely variable; remaining normal for a number of days, then rising to 103 or more. April 10, 1918, the patient was apathetic, the tongue was coated, the face cyanotic. The heart rate was slow and regular. The lungs were clear. The abdomen showed a slight tenderness in the right lower quadrant and right costovertebral angle. Skin spots, about one-fourth inch in diameter, rather bright red, disappearing on pressure, were present, for the most part on the abdomen, chest and back. These papules were much like the roseolae of typhoid, but larger. A blood culture was made. Infection of the right renal tract, atypical typhoid or a sepsis, either cryptogenic or arising from the tonsils, teeth or sinuses, were discussed as possibilities. April 17 the blood culture was reported positive for gram-negative diplococci. There were no signs of meningeal irritation. Many rose-colored spots continued to appear.

A diagnosis of meningococcus sepsis was made and active specific serum treatment begun. April 17, 110 c.c. of antimeningococcus serum were given intravenously. This was followed by chill and other signs of mild anaphylaxis. The following day the patient got out of bed, seemed better, received another intravenous injection and had a severe chill following it. In all, four intravenous injections of serum of 100 or 110 c.c. each, were given during four days, from April 17 to April 20, with subsidence of the temperature and some slight general improvement. April 25, a severe serum reaction followed. There were large patches of urticaria with swelling of the upper lip and of the ankles, and joint pain. April 28 the serum sickness was pronounced. On the following day there was a sudden change in the picture. Headache became intense and was not controlled even by morphin. Large purpuric spots appeared over the feet and legs. Forty-five c.c. of clear spinal fluid were removed under pressure. The cell count was 145. Globulin, pus cells and gram-negative diplococci were found. The patient rapidly developed the picture of a very severe cerebrospinal meningitis. After being in a critical condition for twenty-four hours he responded to vigorous intravenous and

intraspinal serum treatment and finally made recovery after a rather prolonged convalescence.

CASE 5.—*Local Extrameningeal Meningococcus Lesion in the Pleura without Meningitis.* The patient, S. R., aged 23, a private, was admitted to the base hospital, Camp Jackson, S. C., Nov. 17, 1917, complaining of a cold and pain in the chest, eyes and back. The temperature was 103; the pulse, 116. December 26 there was a vague eruption which was observed by the dermatologist, but on which no definite opinion was given. During the first week the temperature varied between 100 and 103. October 24 a bronchitis was discovered. November 28 a left pleurisy developed. On the following day a bronchopneumonia was discovered which subsided after a few days. Later this recurred and on December 4 signs of fluid were found at the base of the left chest. Exploratory puncture revealed a rather thick serous fluid of which 500 c.c. were aspirated. December 6 measles developed from which a very satisfactory convalescence was made until January 10, when there was a return of fever and pain in the left chest. January 14 an empyema was discovered. A left thoracotomy was performed by Major Meredith and the patient made a gradual but satisfactory recovery, being discharged from the hospital March 11. The purulent fluid aspirated from the chest January 14 showed a meningococcus of the regular type.

CASE 6.—*Local Meningococcus Infection of the Sinuses without Meningitis.* The patient, J. M. F., aged 25, a private, was admitted to the base hospital, Jan. 5, 1918, in serious condition, with cough, fever, coryza, cyanosis, tremor and prostration. There was rash which suggested fading measles. The lungs showed a bilateral bronchopneumonia; the temperature was 104.8 on admission and gradually fell, until at the time of death, January 12, it was 101. The pulse and respirations were constantly rapid. Extreme coryza was noted. At the necropsy on January 13 a bronchopneumonia was found. Examination of the accessory sinuses of the nose revealed abscess of the sphenoid and left frontal sinuses and the anterior and posterior ethmoid cells. Pus obtained from the sphenoid sinus contained a meningococcus of the regular type.

DISCUSSION

Cases of which 1 and 2 are types are of great and tragic interest. Of these, some ten have been studied. They present the features of *purpura fulminans*—a sudden onset with chill, moderate or high fever, great prostration, restlessness with apathy, deepening into stupor or coma, which endures until death. The pulse is rapid, running, of small volume, weak and of low pressure. The color is a cyanotic pallor that is a mask of death. The rash begins as purple blotches on the trunk or elsewhere. These increase in size with incredible rapidity until coalescent areas may transform a considerable area of the body surface—even one-third—by ominous purple patches, continually extending until the fatal issue. In addition to the diffuse purpura, punctate petechial spots are thickly sprinkled over trunk, face, extremities and mucosa of the mouth and eyes and seem an independent lesion. No other infection so quickly slays. A nurse did full duty all one morning, felt ill at noon and was persuaded to leave her ward. Twenty hours later she was dead, the skin surface a mass of purpuric splotches. A soldier suffering mild symptoms at

4 p. m., walked into the ward carrying a suit case and not seeming very ill. At 8 p. m. he was dead; the body surface well covered with purpura. Cases of this type have no meningitis either clinically or at necropsy. The spinal fluid is negative and death is the result of the overwhelming sepsis. The blood culture is practically always positive.

In Case 2 the meninges showed a reaction not greater than that observed in the pericardium and not as great as that at times found in those dead from acute infections other than that under discussion. Congestion and increase in mononuclear cells are noted, with a few polynuclears in certain areas, but no free exudate on any of the surfaces. Doubtless here is the very earliest step in a meningitis which would have developed within a few hours into the picture of a local polymorphonuclear preponderance with organisms. Certain is it that at the end of four days' illness the lesions characteristic of epidemic meningitis had not developed, and that death resulted from the general systemic invasion and not from the slight local reaction in the meninges.

In Case 1 death was due entirely to the meningococcemia, there being no indication of meningitis even on microscopic examination of sections from the central nervous system.

In the mind of one who has repeatedly witnessed this picture comes the question if many of the instances of purpura fulminans are not examples of this kind of meningococcus infection. The failure to secure positive bacterial findings in cases of this character heretofore may possibly be explained by the difficulty met in cultivating the meningococcus by the conventional methods. The importance of following such successful technic as that described by Baeslack and his associates³ in the study of the blood of all fulminating purpuras of which the etiology is obscure is emphasized.

Instances of which Case 3 is a type are doubtless rare. It is certain that they are rarely recognized by ordinary laboratory or clinical methods. That the *Diplococcus intracellularis* can cause an acute polyarthritis of a serious septic variety without meningitis has, to our knowledge, not been recognized. Arthritis is a fairly common complication of epidemic meningitis and was observed in about 10 per cent. of our cases. Its occurrence apart from meningitis is but another link in the quite complete chain of evidence establishing the blood stream as the route of meningococcus invasions.

The practical point brought out by this case is that all instances of acute or subacute septic arthritis of which the etiology is obscure should have the benefit of the suspicion of a meningococcemia and

3. Baeslack, F. W., Bunce, A. H., Brunelle, G. C., Flemming, J. S., Klugh, G. F., McLean, F. H., Solomon, A. V.: Cultivation of the Meningococcus, *Intracellularis* from the Blood, J. A. M. A. 70:684, 1918.

the trial of appropriate blood culture methods. The importance of proper diagnosis is apparent in the very satisfactory response to intravenous serum treatment.

Case 4 is a remarkable example of *meningitis tarda* as recently described by French observers (Santon,⁴ Aime⁵). In these cases the symptoms of a systemic invasion of the meningococcus precede by many weeks the final meningeal localization. The features of this long prodromal or premeningitic period are irregular temperature, chills at infrequent and irregular intervals, joint pains, headache, relatively slight prostration, high leukocytosis and polynuclear percentage, tonsillitis and a certain hebetude that characterizes all meningococcus infections. It is probable that some of these cases never develop the secondary meningitis and go on to recovery or fatal issue without recognition (*vide* Case 3). That this case should develop meningitis one week after intravenous treatment for the sepsis may be explained as analogous to the relapsing cases of meningitis. Such relapses are probably from a focus that has not been reached by the earlier course of treatment. The coincidence of this second outbreak with serum sickness corroborates a general impression that the meningococcus thrives in soil prepared by any agent lowering resistance. Santon⁴ describes a case in which meningococcemia dated from May 6, but meningitis did not develop until July 14.

While there is no proof, it is possible that the infection for which the patient, Case 5, entered the hospital and which lasted from November 17 to December 6, when measles developed, was an atypical type of meningococcemia. The irregular temperature, the rapid pulse, the atypical rash with which the staff was not at that time familiar, may possibly be ascribed to this cause. The finding of the meningococcus in the pleural fluid has not been duplicated in this hospital. Captain H. T. Chickering has, however, recovered the meningococcus by lung puncture in a case of bronchopneumonia following measles. This case showed no meningeal symptoms and made recovery.

Pneumonia and pleurisy are common in meningococcus infection both as precursors and as complications of onset or of the later course. A separate report of the pulmonary features of meningococcus infections is in preparation and has been specially studied with First Lieutenant J. Stern, M. C.

The finding of meningococci in the sphenoid and ethmoid sinuses as in Case 6 is not unexpected. Cleminson⁶ remarks that study points to the accessory sinuses as being the main seat of meningococcus

4. Santon: Meningococcemia, Paris méd. 8:86, 1918.

5. Aime, H., and Chene, H.: Parameningococcus Septicemia, Paris méd. 8:118, 1918; Abstr., J. A. M. A. 70:1125 (April 13) 1918.

6. Cleminson, F. J.: Nasopharyngeal Conditions in Meningococcus Carriers, Brit. M. J. 2:51 (July 20) 1918.

infection in carriers. In about 90 per cent. of a series of necropsies on fatal cases of measles in the Base Hospital, Camp Jackson, examination of the accessory sinuses revealed the quite unexpected occurrence of empyema. The meningococcus was found but twice in the pus from this source. Neither patient had history of meningitis.

To call a disease with the wide range of possibilities of infection of joints, pericardium or other body structures epidemic cerebrospinal meningitis is incorrect and misleading. The term epidemic should be abandoned, as there is no difference between the epidemic and sporadic forms. We might as well speak of epidemic measles, or epidemic scarlet fever. The cerebrospinal distribution of the disease is not specific, as infections from the other micro-organisms—tubercle bacilli, *Spirocheta pallida*—have the same localization. Hence we should drop this term cerebrospinal.

The change in nomenclature suggested by Heiman and Felstein⁷ should be generally adopted. As a general term, meningococcus infection should be used. To denote the local processes, meningococcus meningitis arthritis, etc., are brief and satisfactory.

Let us hereafter speak of meningococcus meningitis when dealing with meningococcus infection with predominant cerebrospinal symptoms.

CONCLUSIONS

To emphasize the extrameningeal rôle of the meningococcus, 6 cases are reported in which meningitis was absent or a subordinate part of the disease process. These cases are:

1. Meningococcus sepsis without meningitis either clinically or at necropsy.

2. Meningococcus sepsis without clinical meningitis: at necropsy, meningeal congestion and arachnoid cell hyperplasia—the earliest stages of meningitis.

3. Meningococcus sepsis without meningitis; septic polyarthritis; recovery with intravenous treatment.

4. Meningitis tarda, or meningitis with premeningitic stage of meningococcemia of several weeks' duration.

5. Meningococcus pleurisy, and, 6, meningococcus empyema of accessory nasal sinuses, both without meningitis.

The term epidemic cerebrospinal meningitis should be abandoned.

The term meningococcus infection should be used to denote such general processes as meningococcus sepsis. Meningococcus meningitis should be the term used in the case of meningococcus infection with predominant cerebrospinal symptoms.

7. Heiman, H., and Feldstein, S.: Meningococcus Meningitis, J. B. Lippincott Company, Phila., 1913.

CLINICAL STUDIES ON THE EFFECTS OF LOUSE BITES—*PEDICULUS CORPORIS* *

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MINNEAPOLIS

The previously reported observations of one of us (M.)¹ indicated that a macular erythematous skin eruption, somewhat resembling that of measles or German measles, distributed over the chest, back and abdomen, may occur in a normal person who allows lice to feed on the skin of his forearm only. This eruption was accompanied by general lassitude and malaise, headaches, and peculiar pains in the calves of the legs and soles of the feet, particularly under the toes. Unfortunately the association of these symptoms with louse bites was not at first noted, hence definite data of the illness are not available.

REVIEW OF LITERATURE

An examination of the literature shows that *phthirus pubis* may cause a rise in temperature (Payne²) due to the toxic action of its bites, while it has also been demonstrated experimentally to be the cause of maculae caeruleae. Duguet³ has shown that these spots may also be produced by the inoculation of that portion of the body of the louse in which the salivary glands are located. A number of references appear in the literature to rashes caused by the bites of *Pediculus corporis*, but these are not similar to the rash encountered in our experiments. Prurigo, prurigo senilis, urticaria, and porrigo are grouped together by the editor of the *British Medical Journal* (1869) under the title *Pedicularia*.⁴ More recently, Peacock (1916) refers to "louse rash" as being distressfully common among British troops,

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*A research undertaken for the Medical Division, National Research Council.

1. Moore, W.: An Interesting Reaction to Louse Bites, *J. A. M. A.* **71**:1481 (Nov. 2) 1918.

2. Payne, J. F.: Maculae caeruleae and Other Symptoms Produced by *Pediculi pubis*, *Brit. J. Dermat.* **2**:209, 1890.

3. The New York Medical Journal in an editorial dealing with fatal pediculosis (July 29, 1905, p 234) mentions a worker, Briguet, as offering experimental evidence to show that these macules are due to a toxin secreted by the insects. The work of Briguet cannot be traced, and it is possible that the reference is to the work of Duguet: *Sur les taches bleues: leur production artificielle et leur valeur semeiologique*, *Ann. de dermat. et de Syph.* **10**:545, 1880. Cited from Nuttall, *Parasitology* **10**:378, 1918. *Ibid.*: *Les taches bleues et le pou de pubis*, *Compt. rend Soc. de biol.*, April 17, 1880: *Experiences et recherches nouvelles sur les taches bleues*, *Ibid.* 1882, p. 617.

4. Editorial: *Pedicularia*, *Brit. M. J.* **2**:612, 1869.

but the reference appears to refer to cases of urticaria. In our experiments, although urticaria appeared where the lice were fed (in the cases of S. A. G. and W. G.), the rash encountered on the other portions of the body was quite distinct and could not be classed as a pedicularia. Only in one case (W. M.) was a slight melanoderma present in the area where the lice fed.

Jamieson (1888)⁵ records two clinical observations of young persons infested with lice with a temperature of 103 F. in the one case and 106.2 and 106.4 F. in the other case, which returned to normal after the patient was bathed and freed from lice. After reviewing the literature dealing with the toxic effects of louse bites, Nuttall (1918)⁶ sums up as follows: "Apart from the maculae, phthirus, like *P. humanus*, fleas and mosquitoes, may cause a febrile condition owing to skin irritation, although this appears to be rare; with the removal of the lice, the fever promptly subsides." No mention, as far as can be discovered in the literature, is made of a rash similar to that encountered in our experiments.

EXPERIMENTAL

The present series of observations was undertaken at the suggestion of Prof. Richard M. Pearce, chairman of the Division of Medical and Related Sciences, National Research Council, in order to determine whether the previously recorded observations represented a peculiarity of the individual on whom the lice had fed, or whether it might be regarded as a general phenomenon. There naturally arose the question as to whether the condition represented sporadic typhus fever, trench fever, or some other infection, on the one hand, or a reaction to toxic products derived from the louse. Such a reaction might represent either a primary intoxication or a state of anaphylaxis. In view of the fact that one of the individuals tested had never been bitten by lice before, the rôle of anaphylaxis seems unlikely.

Four perfectly healthy young men, members of the Faculty of the Department of Agriculture of the University of Minnesota, volunteered for the experiments. They were examined by one of us (H) and found to be normal, except in some cases for the enlargement of a lymph gland here and there. The total blood counts, hemoglobin, lymphocytes and differential counts were taken, and the two latter were repeated daily or at frequent intervals. The Wassermann reaction was taken and found by Prof. W. P. Larson to be negative in each case.

5. Jamieson, W. A.: On Some Rarer Effects of Pediculi, *Brit. J. Dermat.* **1**:321, 1888.

6. Nuttall, G. H. F.: The Pathological Effects of Phthirus Pubis, *Parasitology* **10**:375, 1918.

Each of the subjects allowed himself to be bitten twice daily by the number of lice specified. These lice were raised from eggs and had never fed on any except healthy members of the faculty of the University of Minnesota, who volunteered for the work. According to the work of Strong⁷ and his collaborators, and Byam⁸ and his collaborators, therefore, these lice could not be carriers of trench fever.

In every individual bitten, except W. M., there was a prompt rise of temperature ranging from 99.3 to 99.9, after the lice had been fed. Sometimes, as in the case of S. A. G., this occurred with surprising rapidity and the temperature reached 99.6 within an hour after feeding. In every case the afternoon temperature on the first day, six or seven hours after the first feeding, was well above normal and within from one to four days a well defined enlargement of the lymph glands of the axilla was noted. These glands, as well as the inguinal and sub-maxillary glands which also became enlarged, were quite tender in two of the individuals (S. A. G. and W. G.).

Except in the case of W. M., who must be considered to have developed a certain degree of immunity to the bites, having fed lice off and one for over a year, it required from three to eight days for this swelling of the glands to disappear and from four to ten days for the temperature to return to normal. September 27, S. A. G. and W. G., whose condition was then normal, started on a canoe trip. During the trip S. A. G. noted that his temperature had again risen, but having no thermometer the exact temperature is not known. Immediately on his return at 7.30 p. m., September 30, the temperature was taken and found to be 102.7 F. It was noted that all the lymphatic glands previously affected were again enlarged. His temperature remained at from 100 to 101.7 F. for five days after his return, while the swelling of the glands gradually subsided. W. G., who had not fed so many lice nor for so long a period, was not appreciably affected.

In three out of four of the subjects a well defined rash composed of semilunar and crescentic macules from 2 to 3 mm. in size resembling those of a fading measles or German measles occurred. The rash was not very striking and yet was definite enough to be seen without difficulty when it was at its height. The macules disappeared on pressure. It was distributed over the chest, back and upper abdomen, and in no case appeared on the face, neck, arms or lower

7. Strong, Major R. P., and Others: Report on Progress of Trench Fever Investigation, J. A. M. A. **70**:1597, 1918.

8. Byam, Major W., and Others: Trench Fever: A Report of Clinical Observations and Research as to the Etiology, Pathology, Prophylaxis and Treatment of Trench Fever Among Troops, J. A. M. A. **71**:21, 110 and 183, 1918.

limbs. It was always most distinct and persisted longest in the regions between the nipples and the lower costal margins.

In none of the individuals was the spleen palpable, nor was its outline determined by both light and auscultatory percussion sufficiently enlarged to be definite. None of the persons, including Moore himself who was one of the subjects, suffered from the peculiar pains or sensations in feet and legs which had been described by Moore¹ in his previous attacks.

The blood cultures, aerobic and anaerobic, taken by Prof. W. P. Larson when the fever was at its height, were negative.

Three c.c. of the blood of one of the subjects (S. A. G.) was injected subcutaneously under the arm of another individual (R. A. G.). He experienced, within forty-eight hours, a definite rise in temperature to 99.5 and suffered headache and mild sore throat, and diffuse small râles were present in his chest; but this was probably due to an epidemic of "colds" which was rife at the time, rather than distinctly due to anything traceable directly or indirectly to the louse. The following day his temperature was normal and remained below 99 F. for the following two weeks while under observation. This phase of the subject, however, warrants further investigation.

The fact that the condition was transmitted by lice which had never bitten diseased individuals, and that no opportunities existed for inoculation with the feces of the louse, since immediately after feeding, the arm was carefully bathed with alcohol and in some cases treated with ammonia and glycerin, as well as the negative character of the blood culture, point against either typhus or "trench fever." The absence of both positive blood culture, leukocytosis and increase in polymorphonuclear leukocytes, as well as the absence of any foci of pyogenic infection at the site where the lice fed, rule out simple pyogenic infection.

The fact that two of the subjects who had definite papular eruptions at the site of feeding had also fed lice for a certain period of time a year before, while the one person (J. J. W.) who had never fed lice before had no skin eruptions whatever, raises once more the question of anaphylaxis as a possible contributory factor in part of the syndrome. That anaphylaxis was not the only factor, however, is proved by the fact that he, too, had fever and glandular enlargement just as did the others.

While we cannot regard it as proved conclusively, the results of the foregoing observations point more strongly toward the presence of a substance in the louse sufficiently toxic to give rise to a generalized skin eruption and mild fever. This may or may not be protein in nature. The absence of any regularly occurring wheal or similar

lesion at the site of the feeding demonstrates that it probably is not a local irritant like those inserted by bees and mosquitoes, and it is probably not one of the lower organic acids.

The subject must be investigated further before any conclusions regarding this can be drawn.

On the other hand, it was quite clear that for the general health of the individual the bites of lice, even when "home grown," is not an indifferent matter, but greatly impairs his health and bodily vigor. In three of the individuals it was found, as might have been expected, that even relatively mild exercise such as an hour's walk or a morning working in the garden caused the temperature to rise up to 99.8 or 100.6 F. at times when it had been remaining below normal; while in one case more strenuous exercise after apparent recovery caused the temperature to soar to 102.7 F. with swelling of the glands. Accompanying these conditions in all cases a feeling of feverishness and weakness was experienced. The bodily vigor of all these individuals living in their normal excellent environment was therefore much impaired. Had they been living the life of soldiers, their bodily efficiency would surely have been impaired to a much greater extent. If it should appear from subsequent experiment that second and later infections with lice give greater response than first infections, this would only serve to enhance the importance of the question from a military standpoint. From any standpoint, whatever, it becomes obvious, as a result of these experiments, that men who are subject to louse bites have a lower mental and bodily vigor, and that, other things being equal, a louse-free army would be considerably better fighting men than the same army louse-infested.

CLINICAL OBSERVATIONS

CASE 1.—Aug. 27, 1918. W. M., associate professor of Entomology, University of Minnesota; aged 31; married.

Family History.—Father died at 70 with acute Bright's disease. Mother died of apoplexy at 65. The patient had eight brothers and sisters; all died of scarlet fever in childhood, except one sister, who died of Bright's disease at 45, and another sister still living and well. No members of the family have had skin disease, but all three of his children have eczema, which the patient says is inherited from their maternal ancestors.

Personal History.—Scarlet fever at 2½; no kidney trouble, no sequelae; measles at 12; chickenpox at 17; blood poisoning at 24, following a splinter in the finger; no other complications or skin eruptions. This took place while patient was in South Africa, where he remained for three and a half years and was well otherwise. He returned to this country five years ago. At 27 he had grip, followed by inflammation of the right kidney (Dr. E. K. Green and F. S. Bissell). He had some pus in the urine. This was regarded as secondary to the grip. At 30 he had grip again, and then developed an infection in the left antrum which was repeatedly punctured. At 31 he had an infected tooth removed and also tonsils removed. Since then has been well, except for the present illness. No venereal illness.

Present Illness.—He was perfectly well until the first week of May, 1918, when he began to feed 700 to 800 lice twice daily. On May 7, he began to have malaise, headache and indefinite pains all over the body. A rash similar to that of German measles soon developed and was especially marked over the shoulders and abdomen (German measles was prevalent in the community at the time). He thinks that he had a mild fever. This lasted about three days. He returned to normal and resumed the feeding of the lice. He had no further symptoms until May 28, when an attack similar to the first one developed, with a temperature rising to 102 F.

No glandular enlargement was found during this attack, nor was any enlargement of the spleen noted (A. D. H.).

The patient says that the onset of attacks of this illness was gradual; beginning with a general tired feeling, particularly noticeable in the calves of legs and down the shin bone and underneath the soles of the feet, particularly in the phalangeal region, but not specially on moving the joints. It was worse after going to bed—severe enough to keep him awake. This continued a week or more before he became sick and before he noticed the onset of the fever. About the same time he noticed a dull feeling in the head which developed into a definite headache at the height of the disease.

He was never nauseated; but lost appetite for about two days at the fastigium; never vomited; no nosebleed.

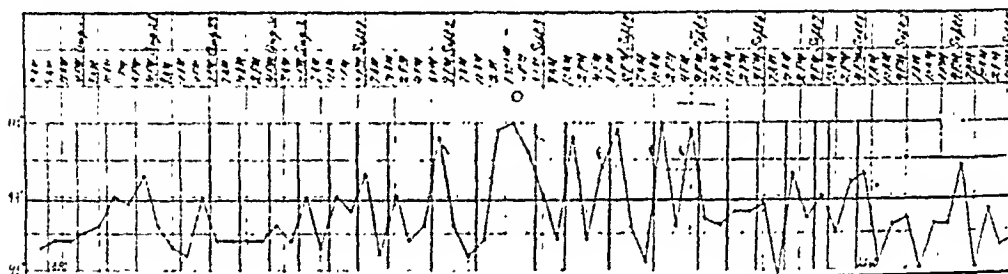


Chart 1.—Rectal temperature curve of W. M. Vertical lines represent louse feedings; the number of lice given at start and finish; O represents occurrence of rash, and E when exercise was taken.

At the fastigium he had pains in the joints, worse on moving them, but the joints were never swollen or tender on touching or on pressure.

The urine was neither much increased nor decreased; nor did he have to void at night more than usual. Apart from a little local erythema lasting only during time the patch is worn, the patient has had no eruption at the site where patches of louse killing substances have been worn.

Physical Examination.—The patient is a tall, well nourished individual, of good, though rather sallow color. The gums and mucous membranes are of good color; sclerae clear; no glandular enlargement present anywhere; tonsils absent; pharynx slightly reddened. Thyroid normal; no tracheal tug. Lungs clear on auscultation and percussion.

Heart dulness extends 4.5 cm. to right of midline and 9 cm. to the left. Sounds clear. Blood pressure 110-80; pulse rate 64; arteries not sclerotic. Abdomen negative. Liver reaches to the costal margin in mammillary line; not palpable. Spleen not palpable. Dulness 8 by 4 cm. No areas of spasm, rigidity or tenderness. Shins clear; joints normal; no tenderness anywhere in joints or muscles, though patient complains of a tired feeling in the calves of both legs in the last couple of days.

Over the anterior surface of the left forearm where the lice are fed there is a very faint macular eruption somewhat resembling measles in its appearance. The spots disappear on pressure. About the bend of the elbow, this

is absent and it is absent from the right arm, which is not used for feeding. This eruption is fainter, but otherwise similar to the eruption present at the height of the febrile illness mentioned in the history. The Wassermann reaction is negative.

Blood Count: Red blood cells 4,400,000; hemoglobin 80 per cent.; leukocytes 7,100; polymorphonuclears 70 per cent.; lymphocytes 22 per cent.; large mononuclears 3 per cent.; transitionals 1 per cent.; eosinophils 4 per cent. Urine clear, straw colored, acid; specific gravity 1.016; no albumin, no sugar; a few epithelial cells present.

Sept. 3, 1918. For the previous three days the patient has had more or less biparietal and vertical headache, as well as a sort of dazed or confused sensation in the head, and a general tired feeling in the legs from the knee down; no definite pains in the feet. He has not been sleeping well. Chart 1 shows the temperature record. At present the temperature is 99.8 F. (rectal); pulse rate regular, 72. Blood pressure, maximal 122; minimal 90; heart not enlarged; sounds clear. The spleen is not palpable and does not reach the costal margin; dulness 10 by 4 cm. Liver not palpable. Glands not enlarged.

Over the lower part of the chest in front and between the shoulders and over the area of the insertion of the diaphragm there is a very faint macular erythema similar in appearance to that present over the anterior surface of the left forearm. Over the right forearm none is visible.

Blood count, September 4, leukocytes 6,700; polymorphonuclears 68 per cent.; lymphocytes 28 per cent.; large mononuclears 3 per cent.; transitionals 1 per cent.; no eosinophils seen in 100 cells counted.

CASE 2.—S. A. G., assistant in Entomology, University of Minnesota; aged 27; unmarried.

Family History.—Father and mother living and well. Three sisters and two brothers all alive and well.

Personal History.—Measles, chickenpox and whooping cough as a child; no scarlet fever or diphtheria or typhoid fever; rheumatism uncertain. As a child the patient was jaundiced and his digestion was easily upset. He is subject to mild tonsillitis and grip and light colds in the winter; but no other illnesses. Does not have asthma, but has had eczema on eye and thumbs both summer and winter, for which he has been treated by Dr. Franklin Wright. No hives or angioneurotic edema. He is not susceptible to poisoning by poison oak. In the winter of 1918 he had an abscess in the left groin, which came without apparent cause, and was opened. There is no history of venereal diseases.

The patient fed the lice used in this series of experiments for about four months in 1917. During the first month, there was no sign; then a red papular eruption would appear at the site of feeding, appearing immediately after feeding and lasting throughout the months in which feeding continued. After he stopped feeding them, it subsided within a week.

The patient began feeding the lice Sept. 9, 1918, at 9:30 a. m., at which time his skin was perfectly clear. Feeding lasted about half an hour and when the lice were removed his arm was covered with the red papular eruption mentioned later.

The temperature (rectal) taken yesterday (September 8) was from 98.1 F. to 99, but now (September 9) has gone to 99.8 at 1 p. m. At 10 a. m. (September 11) it was 99.6 just after feeding the lice, but today (September 10) at 7 a. m. it was 98.4. He has no headache, and does not feel chilly or hot, and does not feel quite as strong as normal. No pains in legs or other peculiar feelings.

Physical Examination.—This shows a well nourished man of good color; pupils equal and react to light and accommodation; color good; tongue clean; throat not reddened. Thyroid not enlarged; no eye signs of exophthalmic goiter (Basedow's disease).

There is no general glandular enlargement, but the left inguinal glands are slightly enlarged. Thorax well formed, symmetrical; lungs clear on auscultation and percussion. Heart not enlarged; extends 4.5 cm. to right; 10 cm. to left. There is a soft systolic murmur over the apex, not transmitted; no murmurs over the base. Blood pressure, maximal 110, minimal 80; pulse rate 104. (Patient says that he usually has a rapid pulse.)

Abdomen negative, liver and spleen not enlarged or palpable; splenic dullness 8 by 4 cm. No rigidity or tenderness.

Skin: In the left inguinal region there is a scar of the abscess previously mentioned. No areas of eczema are now visible.

Over the left leg there is a group of large scars due to an old compound fracture. The right shin and leg are clear, as are also the chest, back, abdomen and right forearm.

Over the entire anterior surface of the left forearm there is an irregular, red, macular and maculopapular eruption which is not infiltrated or hemorrhagic. The red color disappears on pressure. The blotches vary from 2 mm. to 5 cm. in diameter. This eruption corresponds sharply to the areas where the lice feed.

Urine, straw colored; specific gravity 1.020; no albumin; no sugar; many leukocytes.

Blood culture negative. Wassermann reaction negative. Red blood cells 4,272,000; hemoglobin 83 per cent.; leukocytes 7,450; polymorphonuclears 69 per cent.; lymphocytes 30 per cent.; large mononuclears 1 per cent.; no eosinophils (100 cells counted).

Sept. 10, 1918. The patient is quite normal today; temperature normal; feels better than yesterday. The skin eruption has begun to subside and is now more copper-colored and the papules are less raised. This is in spite of the fact that he has fed about 2,000 lice once today and twice yesterday. There is no glandular enlargement. The soft systolic murmur noted yesterday is still present today, but not transmitted beyond the apex. The pulse rate is 92. The spleen is not enlarged and not palpable.

Sept. 12, 1918. Heart sounds as before; no further enlargement of heart, liver, spleen or glands. The eruption on the left forearm has now become confluent, somewhat infiltrated throughout, and the papules are slightly higher than before. The patient now complains of pain along the inner surface of the upper arm 6 cm. above the elbow near the course of the brachial vein, where a small lymphatic nodule less than 5 mm. in size can be felt. The epitrochlear lymph gland is not palpable, nor is the brachial vein. Leukocytes 9,180; polymorphonuclears 89 per cent.; lymphocytes 11 per cent.

Sept. 14, 1918. The patient does not feel well today. Yesterday the temperature was 100.4 and he did not feel steady on his feet, but he had no headache or other symptoms. Today he feels a little weak.

The rash on his left arm is still present and about as before, except that the infiltration has diminished a little in intensity. The induration felt near the course of the brachial vein has subsided, as has also the tenderness in this region.

Over the chest there is present the faintest, just discernible eruption in discrete and confluent faintly pink macules from 2 to 5 mm. in diameter. These become pale on pressure. This is not present over the right arm. It is barely distinguishable over the back; not at all over the abdomen or elsewhere on the arms.

The epitrochlear glands and posterior cervical lymph glands are not palpable, but the left axillary glands are enlarged and tender. The submaxillary glands are enlarged and quite hard on both sides and the glands in both inguinal regions are definitely enlarged.

The spleen is not palpable and its dullness covers the same area as before. The heart has not changed. Leukocytes 6,150.

Sept. 15, 1918. Yesterday morning, just after the examination, the patient began to feel pains on the medial side of left arm just above the bend of the elbow and extending up about half way to the axilla. Last night he was awakened during the night by pain under the axilla. Occasionally this extended down the left axillary region. There was no headache or pain in shins or feet. Today he still feels this pain and feels rather weak.

Today there is definite scaling over the area of eruption on the left arm, the infiltration of which is somewhat harder than before, but the area appears less edematous and is somewhat shrunken.

The epitrochlear glands are not palpable, but the left axillary and anterior cervical glands and the right axillary and the submaxillary lymphatic glands are palpable and sore, and the left posterior cervical and axillary glands are enlarged and palpable. The spleen is not palpable but the area of dulness seems slightly enlarged—9.5 by 5 cm.

Temperature is now 99.8 and pulse rate 90. The heart area and sounds are unchanged.

There is a just discernible maculation of discrete macules (from 2 to 3 mm.) over chest and back and especially over the abdomen. Though visible to several of the observers, it would not be sufficient to attract attention of a casual observer. Three c.c. of blood from the median basilic vein were injected under the skin of R. A. G.

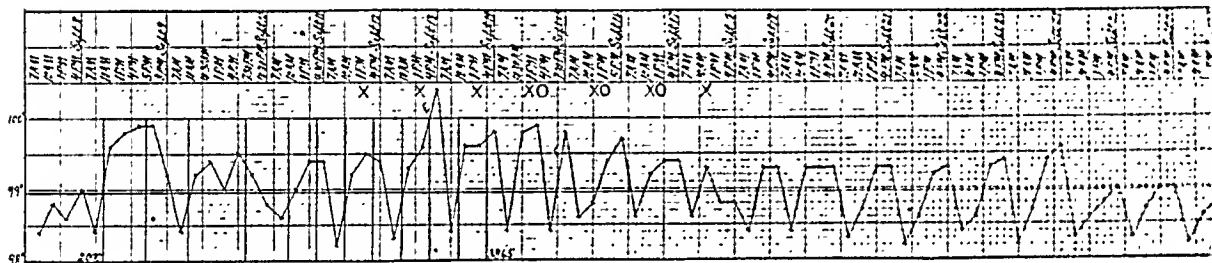


Chart 2.—Rectal temperature curve of S. A. G. Markings same as in Chart 1, with X representing swelling of glands.

Sept. 16, 1918. The rash has faded over the chest and the forearm eruption is gradually drying up. The lymphatic glands are still tender and enlarged, though somewhat less so than yesterday.

The patient took a walk yesterday afternoon. Before the walk the temperature (at 4 p. m.) was 98.4. He walked 4 miles, ate supper and then took his temperature at 7:30 p. m., when it was 99.8. At that time he felt tired and not as strong as usual.

Spleen not palpable—8 by 4 cm. Pharynx slightly reddened.

Sept. 17, 1918. The patient feels a little better. The temperature has not gone above 99.4. The glands are still somewhat tender, but less so than yesterday. The erythema has diminished to the point of being barely visible. Leukocytes 7,450; polymorphonuclears 61 per cent.; lymphocytes 33 per cent.; large mononuclears 3 per cent.; eosinophils 3 per cent.

Sept. 18, 1918. Feels well again; rash has faded. Temperature 98.8 at 1 p. m.; 99.3, however, at 11 a. m. The glands have diminished in size and soreness, but still are a little sore. The spleen is not palpable. The rash on the arm is drying up. The pharynx and pillars of the fauces are slightly injected. This is, however, often present with the patient under normal circumstances. Leukocytes 7,500.

CASE 3.—W. G., engineering student, aged 19; unmarried. (Brother of S. A. G.)

Personal History.—The patient had had measles, chickenpox and mumps as a child; diphtheria at 6; no scarlet fever or rheumatism; no skin diseases

or asthma; occasional attacks of tonsillitis, for which the tonsils were removed four years previously. At the same time adenoids were removed. Varicose veins were removed two years prior to the experiments.

Physical Examination.—(Sept. 12, 1918.) A well nourished young man of good color. Pupils are equal and react to light and accommodation. No eye signs of exophthalmic goiter (Basedow's disease). Thyroid gland just palpable; no general glandular enlargements, but the right epitrochlear and both inguinal glands are enlarged and palpable.

Blood Count Sept. 12, 1918. Red blood cells 4,256,000; hemoglobin 84 per cent.; leukocytes 9,250; polymorphonuclears 75 per cent.; lymphocytes 17 per cent.; large mononuclears 5 per cent.; transitionals 0; eosinophils 3 per cent.

Urine straw colored, acid; specific gravity 1.028; no albumin, no sugar; ten leukocytes seen in specimen examined; Wassermann reaction negative.

Sept. 13, 1918. This morning the patient's temperature was 98.1. At 9 a. m. he fed the lice for fifteen or twenty minutes and at 10 a. m. the temperature was 99.1. At 1 p. m. it was again 98.6. When seen at 2:15 p. m. the skin of his left arm was normal; over the chest, especially below the level of the nipples, there was a very faint, just discernible patchy erythema in patches from 0.5 to 1 cm. in area of the measles type, which was not discernible yesterday.

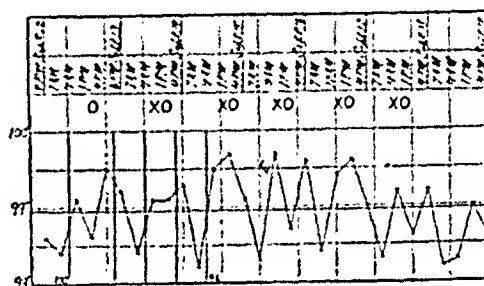


Chart 3.—Rectal temperature curve of W. G. Markings same as in Charts 1 and 2.

The dermatographia seems a little more marked than yesterday but does not bring out the rash mentioned either along its borders or in its vicinity. The spleen and glands are as before.

Sept. 14, 1918. The rash seems more definite today, but is still not definite enough to attract attention. Its presence was confirmed by several independent observers. Leukocytes 9,250. The right epitrochlear gland is still palpable, as are also now the axillary and inguinal glands and the submaxillaries. The spleen is not enlarged.

The area of the forearm corresponding to last night's feeding now shows numerous red infiltrated papules about 3 mm. in diameter. The area of this morning's feeding shows nothing.

Sept. 15, 1918. The rash is about the same as yesterday. The right epitrochlear gland and the axillaries and inguinals are still palpable. Spleen not enlarged; area of dulness 8.5 by 4.5. The erythema is about as before.

Sept. 16, 1918. The patient dug potatoes all morning. At noon he felt some malaise and less well than before. He had headache and felt tired, weak and sick, but there was no nausea or vomiting.

The eruption was still just discernible. The lymph glands were still enlarged and tender. Leukocytes 8,450.

Sept. 17, 1918. Better than yesterday. At 1 p. m. today the temperature was 99.6; physical examination about as before; leukocytes 7,300; polymorphonuclears 69 per cent.; lymphocytes 24 per cent.; large mononuclears 5 per cent.; transitionals 1 per cent.; eosinophils 1 per cent.

Sept. 18, 1918. Ever since the day after starting the feeding the patient's bowels have moved from five to ten times daily; the stools being light brown and liquid. The glands are still somewhat enlarged; rash is almost gone; spleen not palpable; leukocytes 7,300.

CASE 4.—J. J. W., assistant professor of plant chemistry; aged 28; married; two children.

Family History.—Mother died of phthisis; father and one sister living and well.

Personal History.—Measles, whooping cough, chickenpox and vernal ophthalmia (pink eye) as a child; no scarlet fever, diphtheria, rheumatism, tonsillitis or arthritis; with exceptions noted, always healthy; no hay fever, but has a peculiar skin rash. No boils; does not void at night; bowels regular; Wassermann negative. Red blood cells 4,136,000; hemoglobin 84 per cent.; leukocytes 4,850; polymorphonuclears 68 per cent.; lymphocytes 27 per cent.; large mononuclears 4 per cent.; transitionals 1 per cent.

Urine straw colored, neutral; specific gravity 1.025; a trace of albumin is present; no sugar.

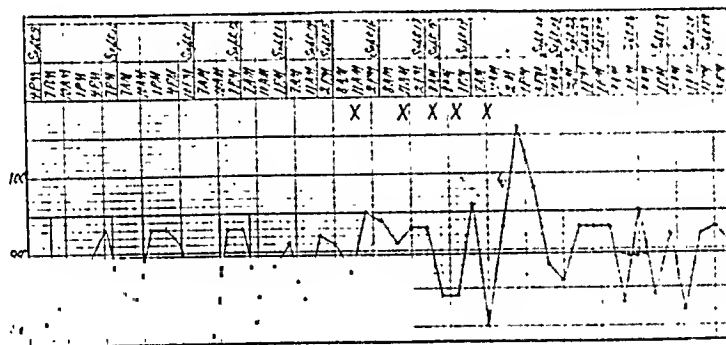


Chart 4.—Rectal temperature curve of J. J. W. Markings same as in Charts 1 and 2. Grip developed September 30 and temperatures were no longer taken.

The patient is a rather sallow individual; pupils are equal and react to light and accommodation; slight pterygium in left eye; no eye signs of exophthalmic goiter (Basedow's disease). The thyroid is palpable but no masses or nodules can be felt. The tongue is clean; throat not reddened. Except for a palpable left epitrochlear gland, which is hard and spotty, and a few palpable left inguinal glands, there is no general glandular enlargement.

Thorax well formed and symmetrical; lungs clear on auscultation and percussion.

Heart not enlarged; apex not prominent; dulness extends 4.5 cm. to the left; sounds clear. Blood pressure, maximal 110; minimal, 84; pulse rate 76.

Abdomen negative; low dulness reaches to the costal margin but the liver is not palpable; the spleen is not palpable; dulness by auscultatory percussion, 8 by 4 cm.

Skin clear except for an area of thickening and brownish induration under the left knee. No scaling or weeping. This patch is apparently eczematous. Shins clear.

Sept. 12, 1918. The patient's temperature has been ranging from 98.3 to 99.4 in the morning and is on this date 99.3. His pulse rate is 84; heart sounds clear; heart not enlarged; liver and spleen not enlarged; he has had no skin eruption. Leukocytes 5,400. A blood culture made by Dr. Larson, September 12, was negative.

Sept. 20, 1918. Since the last examination (September 12) the patient's temperature has been ranging between 99.3 and 99.6 every day. He has been hot around the face and head and has felt rather feverish; no headache,

noticeable weakness or mental dulness noted; no pains in the shins; bowels have been regular; no rash has been noted; he has had a cold for about three days of last week, but temperature remained elevated even after the cold subsided. Today there is no skin eruption, but the left epitrochlear gland is palpable, as are also several axillary glands, which are enlarged on both sides. The spleen is not palpable and the dulness has not increased.

CASE 5.—R. A. G., professor of agricultural biochemistry; aged 33; married; four healthy children.

Family History.—Mother died at 59 of pernicious anemia. Father died at 43 of "African Fever." One brother died of scarlet fever at 2 years; two brothers and one sister living and well.

Personal History.—Mumps, whooping cough, chickenpox, measles, and pleurisy in left side in 1907; tonsils removed in 1917; chronic catarrh; part of turbinates removed in 1917; no rheumatism; no skin diseases; digestion good. Fed about 300 lice one evening about third week in July.

Physical Examination.—Sept. 15, 1918. The patient is a tall, thin individual of rather sallow color, but without any trace of icterus. His gums and mucous membranes are of fair color. The thyroid is not enlarged. The tongue is coated.

The chest is symmetrical and clear on percussion, except for a slight impairment of resonance in the lower part of the left axilla. A few râles are heard throughout the chest. The heart is not enlarged. Dulness extends 5 cm. to the right of the midline and 10 cm. to the left. The sounds are clear.

The abdomen is negative. The liver and spleen are not felt. Splenic dulness, as revealed by auscultatory and light percussion, extends 10 by 5 cm., but does not reach the costal margin.

The inguinal and right submaxillary and right axillary lymph glands are palpable. The epitrochlear glands are not palpable. There is no skin eruption. The leukocytes now number 5,000; polymorphonuclears 71 per cent.; lymphocytes 22 per cent.; large mononuclears 6 per cent.; transitionals 1 per cent. (100 cells counted).

Three c.c. of the blood of S. A. G., who at that time had a well defined rash and a temperature of 99.8, were injected under the skin of the upper arm at 12:45 p. m.

Sept. 16, 1918. There was no skin reaction from the blood injection, but the patient's temperature rose to 99.2 (rectal) yesterday. His throat is, however, definitely reddened and there are small diffuse râles present over both fronts and axillae, perhaps concomitants of a general epidemic of "colds" which is rife at the time of the observation. Throat cultures are negative. Wassermann reaction negative; leukocytes 7,250.

Sept. 17, 1918. Erythrocytes 4,576,000; leukocytes 7,350. Differential count: polymorphonuclears 71 per cent; lymphocytes 24 per cent.; large mononuclears 5 per cent.

The cold subsided and the patient had no further symptoms and no eruption. The rise in temperature could not be definitely ascribed to the injection of blood.

ARBORIZATION BLOCK

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Arborization block or impaired intraventricular conduction is dependent on graphic records for its recognition. It is now generally accepted to indicate disease of the subendocardial myocardium¹ and evidences serious functional cardiac disturbance.² The involvement occurs in the subendocardial or Purkinje plexus.

The deflections constituting the initial ventricular complex of the electrocardiogram are termed Q, R, S, and indicate the passage of the electrical impulse through the main divisions of the auriculo-ventricular bundle and their arborizations. These deflections comprise a graphic record which is upright in all leads, is abruptly pointed, and has a narrow base. The normal base width does not exceed 0.10 second.³

Arborization block is recognized by abnormal deviations of the Q, R, S group. These are increased width, notching of the apex, and splintering of the ascending and descending limbs.

The bizarre complex of arborization block is probably due either to impulse transmission through circuitous and aberrant paths or to delayed transmission through normal channels. Experimental and clinical evidence supports the former view. The abnormal complex, constituting the ventricular premature contraction (extrasystole), is well recognized, as is the complex of ventricular tachycardia and the idioventricular complex of complete auriculoventricular dissociation, which simulate the notched and widened Q, R, S group of arborization block. These we know result from ectopic stimuli which arise somewhere in the ventricular musculature and traverse aberrant paths to provoke ventricular systoles. The constancy in form of the deflections of the normal electrocardiogram make the abnormal complexes stand out as striking entities.

The present study was undertaken to determine, if possible, the significance of this disordered mechanism with especial reference to life expectancy.

1. Carter, E. P.: Further Observations on the Aberrant Electrocardiogram Associated with Sclerosis of the Atrioventricular Bundle Branches and Their Terminal Arborizations. *Arch. Int. Med.* 22:331, 1918.

1. Oppenheimer, B. S., and Rothschild, M. A.: Electrocardiographic Changes Associated with Myocardial Involvement. *J. A. M. A.* 69:429, 1917.

2. Robinson, G. C.: The Relation of Changes in the Form of the Ventricular complex of the Electrocardiogram to Functional changes in the Heart. *Arch. Int. Med.* 18:830, 1916.

3. Lewis, T.: *Clinical Electrocardiography*. London, Shaw, 1913, p. 32.

One hundred and thirty-eight patients with arborization block have been examined. The electrocardiographic requirements warranting this diagnosis were, (1) notching of the apex R, (2) splintering of the ascending or descending limb, and (3) in complexes of normal contour, a base width exceeding 0.10 second. These changes are summarized in Table 1.

The electrocardiograms illustrate the types represented (Figs. 1 to 10). The tension of the galvanometer fiber influences the width of the unaltered complex; a loose fiber is capable of giving an increased base width.⁴

The disorders responsible for the development of subendocardial myocardial disease are, (1) infections, (2) degenerative processes, and (3) local nutritional disturbances. These observations are summarized in Table 2.

TABLE 1.—Q, R, S—

Decade	0.06 Sec.				0.07 Sec.				0.08 Sec.				0.09 Sec.				0.10 Sec.				0.11 Sec.			
	Unaltered	Notched	Splintered	Notched and Splintered	Unaltered	Notched	Splintered	Notched and Splintered	Unaltered	Notched	Splintered	Notched and Splintered	Unaltered	Notched	Splintered	Notched and Splintered	Unaltered	Notched	Splintered	Notched and Splintered	Unaltered	Notched	Splintered	Notched and Splintered
11-20	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0
21-30	0	0	0	0	0	1	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	0	0
31-40	0	0	0	0	0	0	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	0	0
41-50	0	1	0	0	0	1	0	0	0	1	3	0	0	1	1	1	0	0	3	1	1	1	1	1
51-60	0	0	0	0	0	1	0	0	0	0	4	0	0	1	1	0	0	0	3	3	3	3	3	3
61-70	0	0	0	0	0	0	1	0	0	1	5	0	0	1	3	0	0	1	3	3	0	0	1	0
71-80	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Endocarditis was the most frequent causative disorder, and occurred in forty-nine of the 138 cases (35.5 per cent.). Its predominance in the earlier decades of life was anticipated; degenerative and local nutritional disturbances dominate the later decades. In order of frequency are cardiovascular-renal disease with hypertension, thyrotoxic adenomas and arteriosclerosis. Exophthalmic goiter occurred in five cases. Only four proved cases of lues were found. In twenty-seven instances no tangible histories or findings suggesting causative factors were obtained.

Exertion dyspnea was a complaint in all cases, and in thirty-one (22.5 per cent.) orthopnea was a dominant symptom. Palpitation on exertion was present in forty-seven instances (34 per cent.). Twenty-two patients (15.9 per cent.) had angina pectoris and in five of these this occurred in aortic disease. Edema of the lower extremities varying

4. Hirschfelder, A. D.: Personal communication to the author.

from slight pitting in most instances to definite swelling with glazed skin in a smaller number, was present in forty-two patients (30.4 per cent.). Only five cases of general anasarca are recorded in this series. Of the edema cases twenty-four (57.1 per cent.) occurred in patients with endocardial valvular disease. The relative infrequency of edema in grave heart disease is very interesting, and emphasizes the importance of adjunct methods in the thorough examination of patients suffering from cardiac disease.

Objectively, the striking feature present in practically all of the cases is the lack of definition of the heart sounds. They are muffled, the normal differentiation between the first and second sounds is absent, and the auscultatory findings of embryocardia are simulated. There was an increase in cardiac dulness in most of our cases, both to the right and to the left of the midsternal line. Auricular fibrilla-

—COMPLEX CHANGES

0.12 Sec.				0.13 Sec.				0.14 Sec.				0.15 Sec.				0.16 Sec.				0.17 Sec.				0.18 Sec.				Cases
Unaltered	Notched	Splintered	Notched and Splintered	Unaltered	Notched	Splintered	Notched and Splintered	Unaltered	Notched	Splintered	Notched and Splintered	Unaltered	Notched	Splintered	Notched and Splintered	Unaltered	Notched	Splintered	Notched and Splintered	Unaltered	Notched	Splintered	Notched and Splintered	Unaltered	Notched	Splintered	Notched and Splintered	
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3
1	2	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	10
1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5
2	3	2	1	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	31
1	5	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	41
0	4	4	1	0	0	1	2	0	3	1	0	0	1	0	0	2	2	0	1	0	0	0	0	0	0	1	0	39
0	1	2	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	7
Total																												139

tion was present in eighteen cases (13 per cent.), and occurred except in one instance in the later decades of life. Four patients had delayed auriculoventricular conduction, that is P-R intervals exceeding 0.22 second. The deflection amplitudes of the Q, R, S group showed that sixty-four patients (46.4 per cent.) had normal values (10 to 15 millivolts), sixty-one patients (44.2 per cent.) had high values, the greatest 39 millivolts, and thirteen patients (9.4 per cent.) had low values, the lowest of which was 5 millivolts. Deflections of high amplitude, largely diphasic, are believed by Carter to be indicative of a definite, totally obstructive, temporary or permanent lesion of one of the branches of the auriculoventricular bundle; those of low amplitude suggest diffuse sclerosis, although they do not preclude localized lesions of the main branch and its arborizations.

No striking changes in amplitude of the final T-wave of the ventricular complex were noted. This wave was negative in eighty-five

cases (63 per cent.), and occurred most frequently in Lead 1 alone, in forty-two cases (49.4 per cent.). Table 3 shows the T-wave negatively in this series. The inversion of the T-wave in Lead 1 is significant, I believe, and of itself indicative of myocardial changes, for in all the electrocardiograms studied in which this observation was noted,

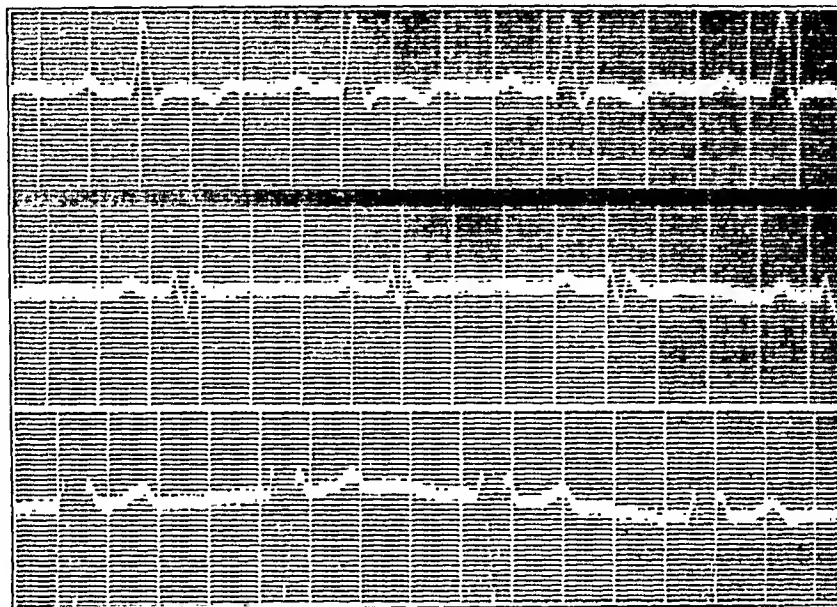


Fig. 1.—Rate 65. Q, R, S complex widened in Leads 1 and 3 0.11 sec. and splintered in Lead 2. Inverted T-wave, Lead 1. Left ventricular preponderance. Case 160997.

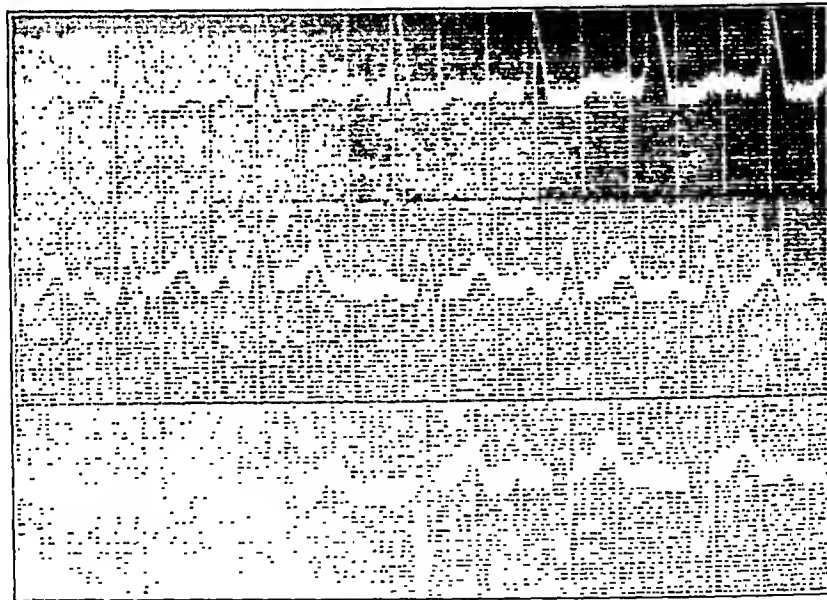


Fig. 2.—Rate 100. Q, R, S complex notched and widened 0.12 sec. Left ventricular preponderance. Case 213193.

the patients presented definite clinical evidence of myocardial insufficiency, except in one case, in which the conclusions were indefinite.

One hundred and twelve patients with arborization block have been heard from in answer to letters of inquiry. Seventy-eight (69.6 per cent.) of these have died; all except three died of heart disease. The average duration of life from the time of examination was eight

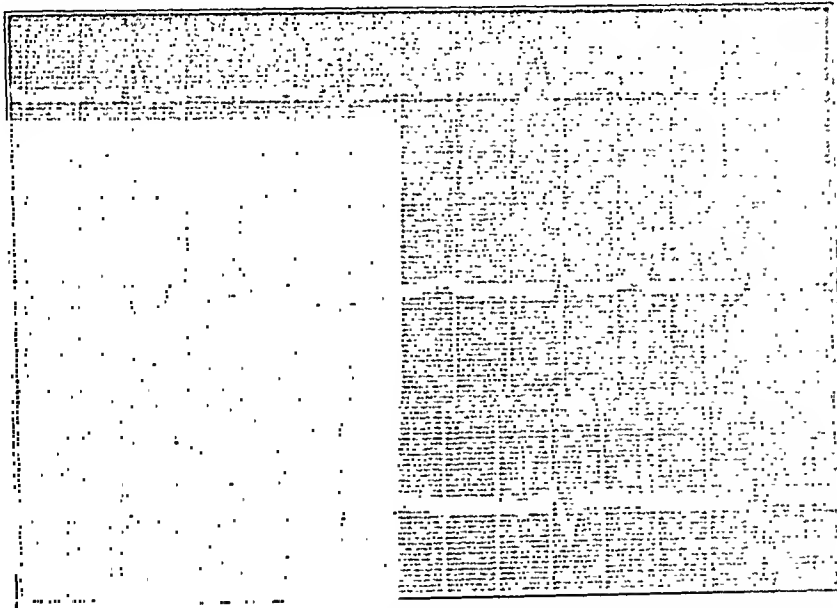


Fig. 3.—Rate 66. Q, R, S complex notched. Left ventricular preponderance. Case 154767.

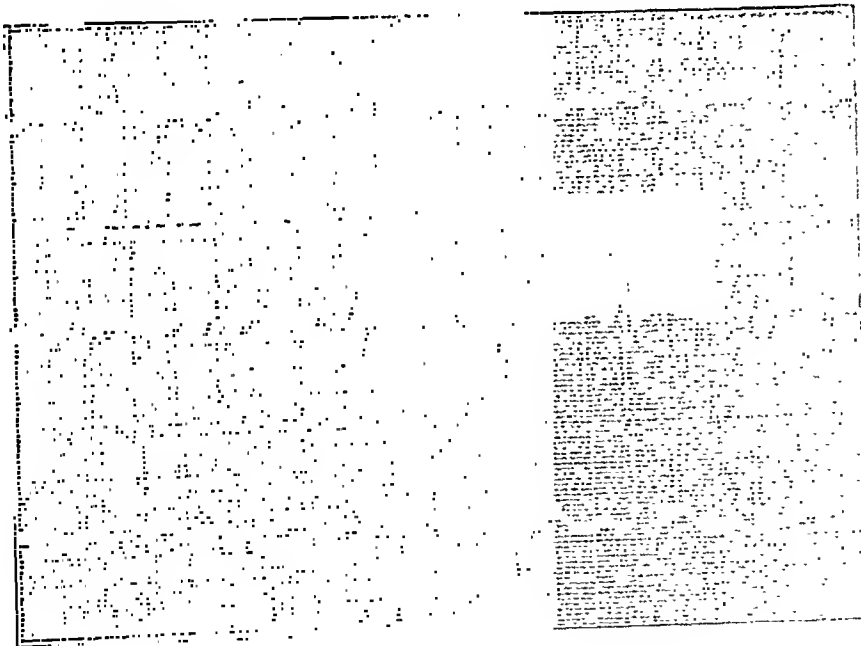


Fig. 4.—Rate 82. Q, R, S complex splintered and widened 0.11 sec. Left ventricular preponderance. Case 165664.

and one-half months. These statistics bear out the presumption that arborization block is a grave disorder. It is well recognized that disease involving the conduction system is a serious menace to life, but arborization block is attended by an earlier mortality than that caused by the lesions higher up. As life is directly dependent on ventricular action, any impairment of ventricular function is grave. The deaths are summarized in Table 4.

Thirty-four patients of the series are known to be alive; of these, seventeen are worse, four of them bed-ridden; nine report their conditions unchanged and eight report some improvement. We were

TABLE 2.—ETIOLOGIC DISEASES

Decade	Endocarditis	Percentage	Cardiovascu- lar-Renal	Percentage	Thyrototoxic Adenomas	Percentage	Exophthalmic Gout	Percentage	Arteriosclerosis	Percentage	Syphilis	Percentage	No Etiologic History
11-20	2	100.0	0	0	0	0	0	0	0	0	0	0	0
21-30	2	80.0	1	10.0	0	0	1	10.0	0	0	0	0	0
31-40	5	62.5	0	0	0	0	0	0	0	0	1	12.5	2
41-50	14	45.2	10	32.3	0	0	1	3.2	0	0	2	6.5	6
51-60	10	24.4	14	34.1	6	14.6	2	4.8	0	0	1	2.4	9
61-70	8	20.5	17	43.6	2	5.1	1	2.6	2	5.1	0	0	9
71-80	2	28.6	2	28.6	1	14.2	0	0	1	14.2	0	0	1
	49		44		9		5		3		4*		27

* Three cases under syphilis classified under endocarditis.

TABLE 3.—T-WAVE NEGATIVITY

Decades	Lead 1	Lead 2	Lead 3	Leds 1 and 2	Leds 2 and 3	Leds 1, 2 and 3	Total
11-20	1	0	0	0	0	0	1
21-30	0	1	2	2	1	0	6
31-40	1	0	3	1	0	0	5
41-50	8	0	1	2	2	0	13
51-60	14	0	3	3	6	1	27
61-70	16	0	3	5	1	4	29
71-80	2	0	0	1	1	0	4
	42	1	12	14	11	5	85

TABLE 4.—SUMMARY OF DEATHS

Decade	Total Cases	Deaths
11-20.....	2	1
21-30.....	10	3
31-40.....	8	5
41-50.....	31	16
51-60.....	41	24
61-70.....	39	23* †
71-80.....	7	6*
Total.....	138	78

* Died of cancer. † Died of pneumonia.

afforded the opportunity of five necropsies; the cardiac findings are appended. No definite localizing lesions were found, but rather diffuse degenerative processes involving the myocardium.

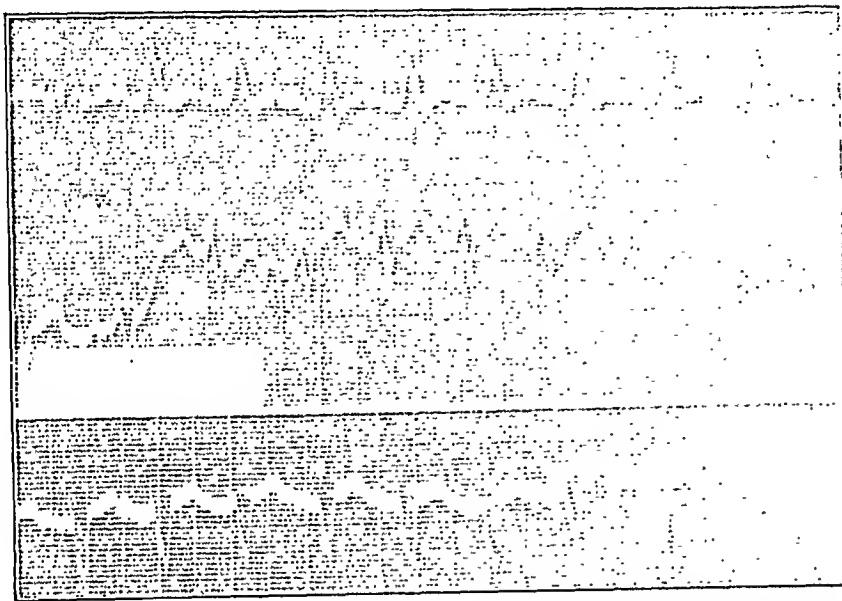


Fig. 5.—Rate 112. Q, R, S complex splintered and widened 0.12 sec. Left ventricular preponderance. Case 176302.

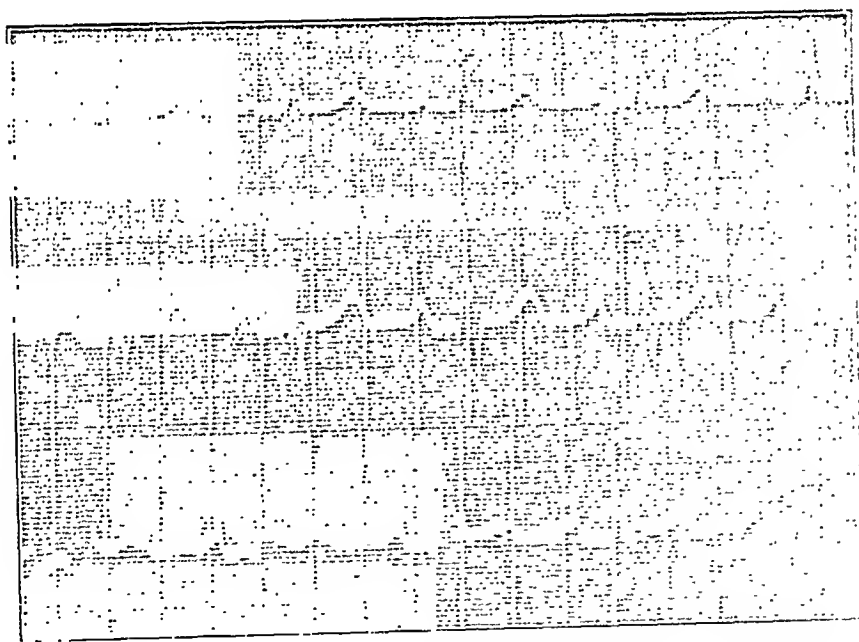


Fig. 6.—Rate 75. Q, R, S complex splintered 0.08 sec. Left ventricular preponderance. Case 162663.

CASE 1 (130119).—Very marked fatty changes in the myocardium; marked dilatation of the aortic, mitral and tricuspid valvular rings of the heart; moderate nodular fibrous and fatty thickening of the lining of the aorta, and of the aortic and mitral leaflets of the heart; marked thinning of the myo-

cardium of the left ventricle; marked dilatation and engorgement of all of the chambers of the heart; moderate hydropericardium. Histologic Findings: Fragmentation and slight fatty changes.

CASE 2 (147045).—Obliterative fibrous adhesive pericarditis; marked nodular sclerosis and fatty changes in the lining of the aorta and its main

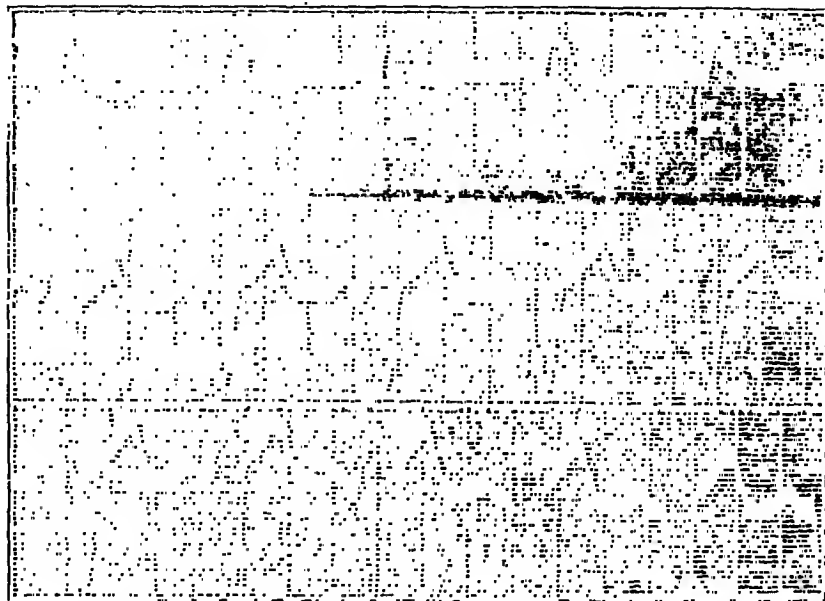


Fig. 7.—Rate 82. Q, R, S complex notched and widened 0.14 sec. Inverted T-wave, Lead 1. Left ventricular preponderance. Case 216281.

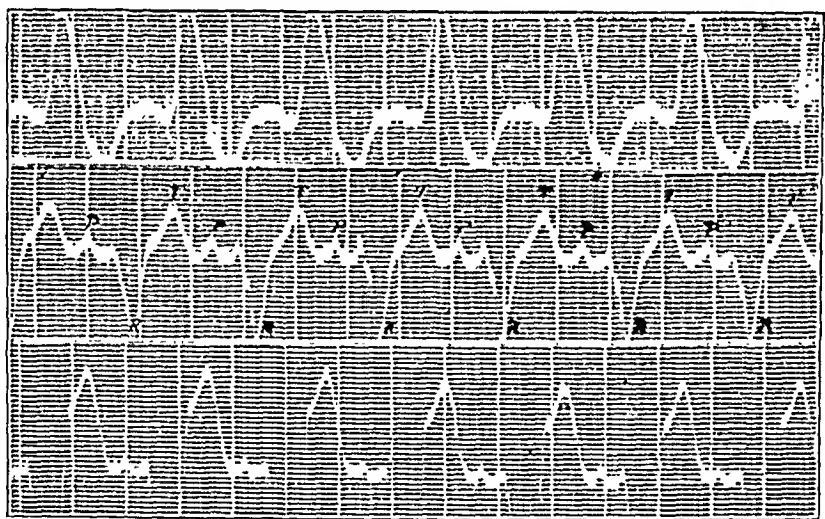


Fig. 8.—Rate 115. Q, R, S complex splintered and widened 0.16 sec. Inverted T-wave Lead 1. Left ventricular preponderance. Case 143010.

branches; marked calcareous sclerosis of the coronary arteries; huge spontaneous thrombosis of the dependent portion of the left ventricle; marked hypertrophy of the myocardium of the left ventricle; marked dilatation of all the chambers of the heart; moderate dilatation of the aortic and mitral valvular rings; marked diffuse thickening of the pulmonary artery. Histologic Findings:

The pericardium was thickened and adherent to the heart. There was a marked replacement of the heart muscle by fibrous tissue. Toward the lower portion was seen hyalinization of the muscle. The thrombus was made up of fibrin and in places showed a slight infiltration of leukocytes. With the fat stain considerable fat was found in the thrombus.

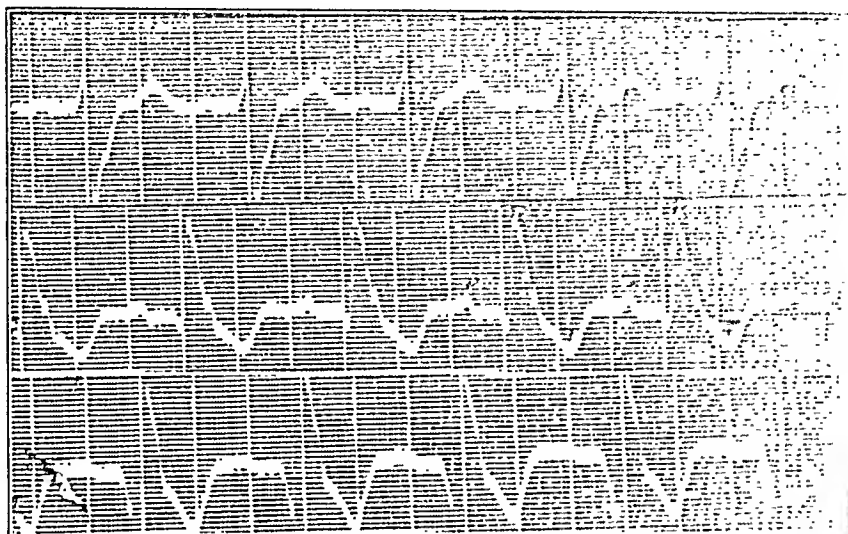


Fig. 9.—Rate 86. Q, R, S complex notched, splintered and widened 0.12 sec. Inverted T-wave, Leads 2 and 3. Right ventricular preponderance Case 142757.

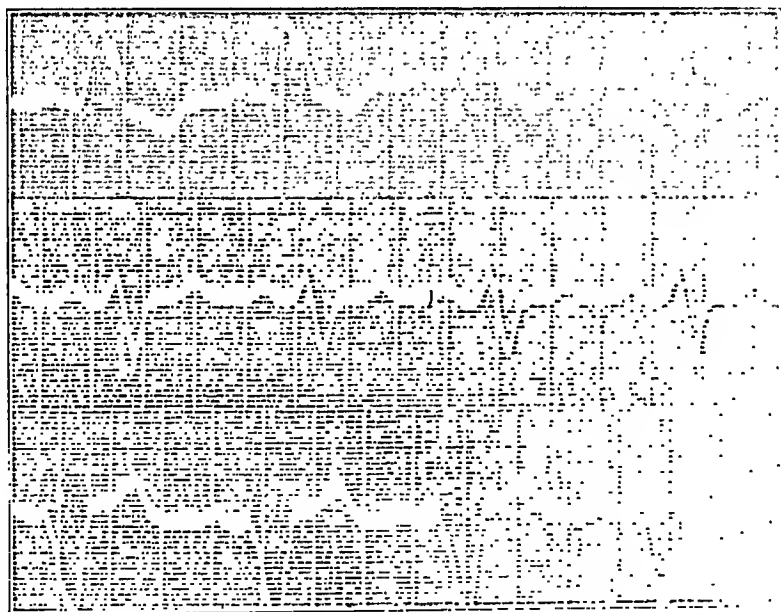


Fig. 10.—Rate 75. Q, R, S complex notched and widened 0.16 sec. Inverted T-wave, Lead 1. Left ventricular preponderance. Case 154081.

CASE 3 (161776).—Marked fatty degeneration of the myocardium; marked hydropericardium; moderate dilatation of the heart. Histologic Findings: In the heart there were marked fatty degeneration and fragmentation; moderate increase in fibrous connective tissue and hypertrophy of the muscle.

CASE 4 (189701).—Acute dilatation of the heart; marked fatty and fibrous sclerosis of the lining of the aorta and of the aortic and mitral valvular leaf-

lets; petechial hemorrhages in the visceral pericardium. Histologic Findings: Moderate diffuse fatty degeneration of the myocardium. Aortitis probably luetic; fibrous and fatty changes in the intima and media, with round cell infiltration.

CASE 5 (197468).—Marked fatty and fibrous diffuse parenchymatous myocarditis; marked hypertrophy of the myocardium of the left ventricle; marked dilatation of all the chambers and valvular rings of the heart; spontaneous mural thrombosis of the left ventricle; slight hydropericardium. Histologic Findings: Fatty and fibrous degeneration of the myocardium.

SUMMARY

1. Arborization block is a grave disorder of the cardiac mechanism; it entails a large and early mortality (69.6 per cent.), in an average duration of eight and one-half months.
2. Disorders responsible for the development of this condition were found to be, in order of frequency, (1) infections, (2) degenerative processes, and (3) local nutritional disturbances.
3. The relative infrequency of edema was a striking observation.
4. The lack of definition and differentiation between the first and second heart sounds was constantly observed.

THE BASAL METABOLISM IN ANEMIA WITH ESPECIAL
REFERENCE TO THE EFFECT OF BLOOD TRANS-
FUSION ON THE METABOLISM IN PER-
NICIOUS ANEMIA *

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AND
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HISTORICAL

In spite of critical reviews of the investigations on metabolism in anemia published by Strauss,¹ in 1906, and Meyer and DuBois,² in 1916, it will be profitable to discuss again the material which has been presented.

1. *Animal Experimentation.*—Work on metabolism in anemic animals has concerned itself almost entirely with posthemorrhagic conditions. Thus Bauer,³ under the complex disturbances immediately following blood loss, found the metabolism slightly diminished; Delchef⁴ found it normal or slightly diminished; Finkler⁵ and Pembrey and Gürber⁶ found it normal; Fredericq⁷ found it transiently diminished and then elevated; Lukjanow⁸ and Hári⁹ found it elevated. Bauer³ reported a remarkably diminished metabolism a few days after bleeding. His work has been justly criticized by Pembrey and

* From the Respiration Laboratory and Medical Clinic of the Peter Bent Brigham Hospital and the Laboratory of Physiology of the Harvard Medical School.

1. Strauss, H.: Cf. von Noorden's Handbuch der Pathologie des Stoffwechsels, Berlin, 1:881, 1906.

2. Meyer, A. L., and DuBois, E. F.: The Basal Metabolism in Pernicious Anemia, Arch. Int. Med. Part 2, 17:965, 1916.

3. Bauer, J.: Ueber die Zersetzungs Vorgänge im Thierkörper unter dem Einflusse von Blutentziehungen, Ztschr. f. Biol. 8:567, 1872.

4. Delchef, J.: Influence de la saignée et de la transfusion sur la valeur des échanges respiratoires, Arch. internat. de physiol. 3:408, 1905-1906.

5. Finkler, D.: Ueber den Einfluss der Strömungsgeschwindigkeit und Menge des Blutes auf die thierische Verbrennung, Arch. f. d. ges. Physiol. 10:368, 1875.

6. Pembrey, M. S., and Gürber, A.: On the Influence of Bleeding and Transfusion on the Respiratory Exchange, Jour. Physiol. 15:449, 1894.

7. Fredericq, L.: De l'action physiologique des soustractions sanguines, Travaux du Laboratoire, 1:133, 1885-1886.

8. Lukjanow, S.: Ueber die Aufnahme von Sauerstoff bei erhöhtem Procentgehalt desselben in der Luft, Ztschr. f. physiol. Chem. 8:313, 1884.

9. Hári, P.: Der Einfluss grosser Blutverluste auf die Kohlensäure- und Wasserausscheidung und Wärmeproduktion, Arch. f. d. ges. Physiol. 130:177, 1909.

Gürber,⁶ who found no changes from the time of hemorrhage until recovery, and their findings are apparently verified by Hári,⁹ who has reported so slight an elevation during the period of recovery as to fall within normal limits. In the experiments of Pembrey and Gürber⁶ the removed blood was at once replaced by saline solution, a procedure which they term "transfusion." Delchef⁴ and Hári¹⁰ have reported the only studies on true transfusion. Immediately after the anemic animal received the injected blood Delchef⁴ found the oxygen consumption greatly elevated, and attributed this to the agitation and dyspnea attendant on the operation rather than to direct effects from increased blood content. Hári¹⁰ found the metabolism somewhat increased on injection of fresh blood into normal animals. His results may also be attributed to the agitation resulting from the operation or to the actual food received by the animal in the form of the injected plasma.

The diversity of results which all these observations record, while undoubtedly due in part to determinations of the metabolism too soon after the excitement attendant on hemorrhage, is largely due to failure on the part of the observers to take uniform and adequate precautions in regard to food, muscular activity and apparatus.

2. *Clinical Observations.*—The same technical considerations coupled with lack of normal standards have caused a large part of the disagreement found in metabolic studies on clinical anemias. On the basis of Meel's formula for surface area and the normal of 34.7 calories per square meter per hour, Meyer and DuBois² have recalculated the basal metabolism on certain clinical anemias studied prior to their own work. They found that not only the pioneer work of Pettenkofer and Voit,¹¹ but that of all authors on leukemia shows a considerably elevated metabolism. They also found that the data of Kraus and Chvostek¹² and Bohland¹³ on anemias in general give values above or on the upper limits of normal. It should be noted that both of these observers provided experimental conditions which are now known to increase the metabolism. Thiele and Nehring¹⁴ have reported a normal metabolism for secondary anemia, but diminished or on the lower border of normal for chlorosis. For their one case

10. Hári, P.: Ueber den Einfluss der intravenösen Bluttransfusion auf den Stoff- und Energieumsatz, *Biochem. Ztschr.* 34:111, 1911; 44:1, 1912.

11. Pettenkofer, M. v., and Voit, C.: Ueber den Stoffverbrauch bei einem leukämischen Manne, *Ztschr. f. Biol.* 5:319, 1869.

12. Kraus, Fr., and Chvostek, Fr.: Ueber den Einfluss von Krankheiten, besonders von anämischen Zuständen, auf den respiratorischen Gaswechsel, *Ztschr. f. klin. Med.* 22:449, 1893.

13. Bohland, K.: Ueber den respiratorischen Gaswechsel bei verschiedenen Formen der Anämie, *Berl. klin. Wchnschr.* 30:417, 1893.

14. Thiele, O., and Nehring, O.: Untersuchungen des respiratorischen Gaswechsels unter dem Einflusse von Thyreoideapräparaten und bei anämischen Zuständen des Menschen, *Ztschr. f. klin. Med.* 30:41, 1896.

of pernicious anemia our computations, also based on Meeh's formula and 34.7 calories, show a gradual and unexplained drop in metabolism from the upper to the lower border of normal over a duration of two weeks. The anemias studied by Magnus-Levy¹⁵ show a normal calorific output, with the exception of a slight elevation in one case of pernicious anemia and an equally slight diminution in one case of secondary anemia. He also found a small drop in metabolism in two chlorotic, one secondary and one leukemic case under treatment with iron preparations, and under the same conditions a slight rise in one of secondary anemia. Basing their computations on modern standards, Meyer and DuBois² found their own cases of pernicious anemia gave a metabolism on the upper limits of normal in mild types, and definitely elevated in severe ones. Their worst case, on observations repeated over an interval of time, showed a drop in metabolism accompanied by a fall in temperature and pulse rate. Grafe¹⁶ and Eberstadt¹⁷ attempted to correlate the blood forming ability of anemic animals with the metabolism. They found that rabbits with exhausted marrow from hemorrhagic anemia or from anemia due to phenylhydrazin injections had diminished metabolism, while those anemic but with normal marrow showed normal metabolism. Rolly¹⁸ contradicts these findings on animals and adds observations on clinical anemias. Our computations of his figures, again based on Meeh's formula and 34.7 calories, show a metabolism considerably elevated for pernicious anemia and for an aplastic type of anemia due to carcinoma, on the upper level of normal for chlorotic and hemorrhagic anemia, on the lower level for secondary anemia due to lead poisoning, and diminished for one due to parasitic infection. Grafe,¹⁹ stimulated by his animal work to belief in the influence of active blood formation in increasing metabolism, carried his observations into the clinic. Contrary to Rolly¹⁸ he suggested that the same relation seemed to hold, since two of the most severe cases of pernicious anemia with signs of marrow insufficiency gave the lowest values in his series, and a third case gave a much higher metabolism during a blood crisis than subsequently when regeneration was less active. According to our computations, the two first cases had a metabolism on the lower border of normal.

15. Magnus-Levy, A.: Der Einfluss von Krankheiten auf den Energiehaushalt im Ruhezustand, *Ztschr. f. klin. Med.* **60**:177, 1906.

16. Grafe, E.: Beiträge zur Kenntnis der Kompensations-einrichtungen bei chronischen experimentellen Anämien. München. med. Wchnschr. **51**:2840, 1912.

17. Eberstadt, F.: Ueber den Einfluss chronischer experimenteller Anämien auf den respiratorischen Gaswechsel, *Arch. f. exper. Path. u. Pharmacol.* **71**:329, 1912-1913.

18. Rolly, Fr.: Ueber den respiratorischen Gaswechsel bei chronisch anämischen Zuständen, *Deutsch. Arch. f. klin. Med.* **114**:605, 1914.

19. Grafe, E.: Zur Kenntnis des Gesamtstoffwechsels bei schweren chronischen Anämien des Menschen, *Deutsch. Arch. f. klin. Med.* **118**:148, 1915.

while the third case had an elevated metabolism during the crisis and was normal during the period of moderate regeneration.

It is evident from this review that with the exception of leukemia, no definite conclusions have been obtained concerning the metabolism in anemia. Not only has there been no agreement from case to case, but in one and the same patient with similar experimental conditions, the results have shown wide variations; and unfortunately the time relations of metabolism determination to clinical treatment and blood picture in any such case have not been sufficiently noted to make explicable the changes seen from date to date in the calorific output. On the whole, however, experimental data have given evidence of a tendency toward increased metabolism in anemias of all types.

Many explanations for this increase have been given. They fall into two groups in relation to the experimental solution of the problem:

1. The increased muscular work required by the more rapid respiration and heart rate have been considered in most cases sufficient to cause such increases in metabolism as have been observed, with the exception of leukemia. This explanation depends on simple muscular compensation and demands no consideration of obscure toxic factors, metabolism of young red cells, etc.

2. The increased metabolism of young and nucleated red cells, unusual numbers of white cells, undetermined toxic influences and activity of the blood forming centers have, with other possibilities, been cited as causes of the increased metabolism. None of these causes is definitely compensatory.

If the grade of the metabolism in anemia is due in any degree to the increased muscular work which the disease requires, it should be possible by reducing the heart rate and respiration to normal to gain a true picture of the uncompensated normal metabolism of the case. Blood transfusion, by an almost instantaneous check to the accelerated heart and lung action in these patients, restrains the muscular compensation. We have been able to find no record of work on the gaseous exchange under these conditions, and as transfusion was being employed by two of us²⁰ in the treatment of anemia, an exceptional opportunity for metabolic study was offered.

EXPERIMENTAL METHODS

1. *Transfusions.*—The technic employed is discussed in a previous article.²⁰ It is of interest to note that the patients have received transfusions of whole blood and transfusions of washed red cells suspended in physiologic salt solution. The effect of both types of transfusion is the same—a decrease in metabolism. It should be noted that in the transfusions of washed red cells

20. Drinker, C. K., and Brittingham, H. H.: Cause of the Reactions Following Transfusion of Citrated Blood, Arch. Int. Med. To be published.

we have provided the simplest possible conditions—an increase in circulating hemoglobin without introduction of material which can be burned, as is inevitable in introduction of plasma.

2. *Metabolism Determinations.*—For the metabolic study a combination of the Douglas and Tissot²¹ methods was employed. The half mask and modified valves as supplied by Siebe Gorman & Co. were used in connection with a modified Tissot spirometer. The latter is made of aluminum, has a syphon counterpoise, but a constant volume water bath so that corrections must be made for the displacement.

Two portable Haldane gas analyzers²² were used for the analyses of the expired air. Duplicate analyses were made on every period of a determination. After each day's analyses, air was drawn through the outdoor tube and analyzed. This checked at once the patient's inspired air and the accuracy of the analyses on his expired air.

Without leaving his bed, the patient was wheeled to the laboratory from fourteen to sixteen hours after his last nourishment—a light supper—and eight or more hours after his last drink of water. There the metabolism nurse took charge of his comfort. He lay on his back with never more than two soft pillows under his head, and with perhaps one under back or knees. Pulse and respirations were taken every three minutes until such time as the chart showed constancy—an interval never less than twenty minutes, usually thirty. The mask was then tied in position and five minutes elapsed before the first period was begun. This was found to be time enough to overcome any effects due to the excitement of the adjustment of the mask. The period was run nine to ten minutes. A kymographic record of the respiration was made throughout and all movements possible of detection were recorded. At the end of the period the mask was removed, the buccal temperature was taken and the patient was permitted to make slight movements. In about ten minutes the mask was again placed in position; this time the patient exhaled into the room for but one minute and a second period was carried through exactly as the first. We prefer this double placement of the mask as it enables us to detect readily any possible leak. When muscular and nervous activity are ruled out and the two periods agree satisfactorily we are sure that the mask was air tight. At the end of the second period the patient's height and weight were taken and he was returned to the ward.

The respiration rate and volume per respiration were established from the pneumographic records. The percentage normality of the metabolism was based on the DuBois linear formula²³ and the corresponding standards of normal calorific output.²⁴ Use of these standards was governed not by our conviction of their finality, but by our belief that at present they form the best basis for presentation of the material we have to offer. The nitrogen metabolism was not studied. The nonprotein respiratory quotient,²⁵ however, was used to compute the total heat production. Benedict²⁶ has shown that

21. Carpenter, T. M.: A Comparison of Methods for Determining the Respiratory Exchange of Man, Carnegie Institution of Washington, Publication 216, 1915, p. 61.

22. Haldane, J. S.: Methods of Air Analysis, London, 1912.

23. DuBois, D., and DuBois, E. F.: A Formula to Estimate the Approximate Surface Area if Height and Weight be known, Arch. Int. Med., Part 2, 17:863, 1916.

24. Aub, J. C., and Dubois, E. F.: The Basal Metabolism of Old Men, Arch. Int. Med. Part 2, 19:823, 1917 (page 831 only).

25. Lusk, G.: The Science of Nutrition, Ed. 3, Philadelphia, W. B. Saunders Co. 1917, p. 61.

26. Benedict, F. G., and Carpenter, T. M.: Food Ingestion and Energy Transformations with Special Reference to the Stimulating Effect of Nutrients, Carnegie Institution of Washington, Publication 261, 1918, p. 203.

such a method of computation ordinarily causes an error in percentage normality of from 1 to 2 per cent. While this could in no way affect agreement between closely following periods, it might easily do so between the results of different days. We, therefore, consider that in order to be significant, a change in the metabolism on different days must show a variation of the averages of at least 5 per cent., while in any one determination the two periods, to be satisfactory, must vary by not more than 3 per cent.

TABLE 1.—METABOLISM STUDIES ON—

Case No. and Name	Med. No.	Diagnosis	Sex	Age	Metabolism		
					Date	Height, Cm.	Weight, Kg.
1 M. C.	7552	Pernicious anemia; chronic type; duration July, 1915 to November, 1917; no remissions	♂	53	11/15/17	164.1	59.9
2 L. A. T.	7793	Pernicious anemia; chronic type; duration August, 1916 to January, 1918; remission September, 1917, to November, 1917	♂	46	1/ 4/18	173.2	70.7
3 J. A. O.	8448	Pernicious anemia; chronic type; duration April, 1917 to April, 1918; yellow pallor of skin noticed first April, 1918; no remissions	♀	62	4/15/18	158.6	49.1
4 A. J. N.	5811	Neeropsy diagnoses: Emaelation; hyperplasia of lymphatics of small intestine and mesenteric glands; atrophy of liver and spleen; congestion of kidney; Meckel's diverticulum. Chronic anemia; duration June, 1915 to January 1917; progressing slowly and without remission	♂	42	1/16/17	175.0	58.4
5 J. F. G.	8473	Secondary anemia; carcinoma of stomach; hypertension; duration of anemia, April, 1917 to April, 1918; progressing slowly and without remission	♂	59	4/12/18	169.1	57.0
6 E. K.	8191	? Pernicious anemia; neuritis; dilation aortic arch; syphilis; fever (cause unknown); duration of anemia, November, 1917 to March, 1918; progressing slowly and without remission	♀	58	3/23/18	158.4	53.3
7 L. K.	6951	Pernicious anemia; chronic type; furunculosis; duration July, 1916 to August, 1917; no remissions	♂	73	8/13/17	165.8	50.4
8 A. H. P.	8220	Pernicious anemia; acute type; duration, February, 1918 to March, 1918	♂	58	3/ 6/18	177.4	67.3
9 F. D.	8624	Pernicious anemia; chronic type; duration January, 1917 to May, 1918; one remission March, 1917 to January, 1918	♀	42	5/10/18	162.0	64.3
10 A. S.	7470	Splenic anemia; splenomegaly; duration of anemia, October, 1916 to October, 1917; progressing slowly and without remission	♀	18	11/10/17	160.2	48.3
11 J. J. M.	8140	Banti's disease; bronchitis; duration of anemia, December, 1917 to February, 1918; no remissions	♂	33	2/28/18	178.0	77.6
12 G. A. C.	7739	Pernicious anemia; chronic type; arteriosclerosis; ventral hernia; duration February, 1916 to March, 1918; remission September, 1917 to November, 1917	♀	59	12/26/17	155.9	41.8
13 W. E. M.	8192	Pernicious anemia; chronic type; laryngitis; duration January, 1915 to February, 1918; diagnosed pernicious anemia January, 1915; had long and rather complete remission during years of 1916-1917	♂	53	3/ 2/18	175.5	59.7
14 T. G. H.	8204	Secondary anemia (brief duration); menorrhagia; duration of anemia, September, 1917 to March, 1918	♀	35	3/ 7/18	164.7	39.5
15 E. F. M.	8217	Pernicious anemia; acute type; duration of anemia, February, 1918 to March, 1918; no remissions	♀	56	3/ 8/18	170.6	59.7
16 A. J. C.	7400	Splenic anemia; splenomegaly; duration of anemia, September, 1917 to October, 1917	♀	60	10/23/17	157.0	56.6
17 E. M.	7586	Secondary anemia; carcinoma of stomach; abdominal metastases; duration of anemia, June, 1917 to November, 1917	♂	41	11/23/17	175.3	55.5
18 E. M. C.	8040	Pernicious anemia; chronic type; febrile and dangerously ill at present; anemia first noted June, 1916; complete remission January, 1917 to August, 1917; gradual decline August, 1917 to February, 1918; death May, 1918	♀	29	2/10/18	150.1	40.7

† The two periods disagreed by 4 per cent.

‡ The two periods disagreed by 6 per cent.

PRESENTATION OF DATA

In the accompanying tables we have given the average data of the two periods of a day's determination and have pointed out cases in which the parallel periods did not fall within the 3 per cent. limit. In most cases a determination of metabolism was made before any type

of treatment was undertaken. Exceptions are noted in Table 3. The metabolism was then followed from time to time during spontaneous improvement or in connection with the transfusions. Of necessity a number of patients received an original determination before treatment, but could be studied no further. Such cases we have placed in

—UNTREATED CASES OF ANEMIA

Metabolism								Blood Picture							
Buccal Temperature, F.	Pulse	Respiration	Volume per Minute, L.	Oxygen Consumption per Minute, C.c.	Respiratory Quotient	Total Calories per Hour	Per Cent. Divergence from Aver. Normal Basal Linear	Date	Hemoglobin, per Cent.	R. B. C., Million	W B. C.	Nucleated R. C.	Anisocytosis	Polkilocytosis	Remarks
98.6	70	9.8	4.02	186	0.75	52.7	-15	11/16/17	98	4.3	6,700	0	++	+	Many macrocytes seen
98.6	67	9.3	4.31	215	0.78	61.5	-13	1/ 3/18	69	2.3	6,000	0	++	++	
98.8	80	14.9	4.56	159	0.75	45.1	-11	4/15/18	30	1.0	5,000	0	++	0	
98.2	69	11.0	4.93	219	0.80	63.1	- 4	1/17/18	73	2.9	6,600	2	+	+	
97.0	69	14.3	6.33	210	0.76	59.8	- 4	4/11/18	50	3.0	18,800	0	+	+	
98.6	72	20.2	4.55	187	0.74	53.1	- 2	3/20/18	60	3.1	4,600	0	+	0	Plate counts: March 29, 1918, 146,000; March 29, 1918, 181,000.
96.8	66	16.7	5.70	193	0.73	54.6	- 1	8/12/17	35	1.5	3,800	16	++	++	10 megaloblasts in the 100 blasts seen in counting 100 leukocytes
99.2	95	16.3	6.00	247	0.77	70.4	+ 2	3/ 7/18	39	0.9	5,000	0	++	0	
99.0	84	16.0	5.84	221	0.77	63.2	+ 5	5/ 9/18	40	2.5	6,100	0	+	+	
98.6	61	19.1	5.22	209	0.73	59.1	+ 5	11/ 8/17	68	3.0	4,800	0	0	0	Splenectomy showed large splenitis
98.6	90	13.5	7.11	203	0.75	83.3	+ 8	2/25/18	75	2.8	3,000	0	0	0	Plate count 66,000; patient died May, 1918; no necropsy
99.4	72	13.7	4.50	182	0.76	51.8	+ 9†	12/23/17	40	1.5	6,700	0	0	0	Plates decreased; patient rarely showed blasts
98.4	71	17.5	6.51	253	0.76	72.1	+11	3/ 2/18	41	1.4	7,000	0	+	+	
99.2	102	18.4	5.11	198	0.74	56.2	+11	3/ 6/18	30	2.2	3,800	0	+	+	Patient recovered with 1 transfusion and iron medication
100.0	101	22.1	6.55	241	0.73	68.0	+15	3/ 7/18	25	0.8	2,500	1	++	++	One megaloblast seen
98.8	97	14.6	5.42	217	0.75	61.5	+15‡	10/22/17	68	3.6	7,000	0	+	+	Patient developed large splenic tumor; death April, 1918; no necropsy
98.8	87	11.9	5.31	265	0.71	74.5	+16	11/20/17	36	3.7	11,400	2	++	++	
102.8	118	17.8	5.50	205	0.75	58.1	+20	2/ 8/18	55	2.1	3,200	0	+	++	

Table 1, together with the original determination of all cases studied during treatment. Table 1 thus tabulates the data of the metabolism studies on our untreated anemias, together with that necessary for an estimation of the clinical picture and for the basis of computations.

Table 2 is so arranged as to show in detail the data and time relations of metabolism to treatment and blood picture in a complete course of study on six characteristic patients.

Table 3 gives the admission and the end data on the remainder of our cases studied during a course of treatment.

TABLE 2.—RELATION OF METABOLISM TO—

Med. No.	Diagnosis	Sex	Age	Treatment	Dates Metabolism and Treatment	Metabolism				
				Description		Height, Cm.	Weight, Kg.	Buccal Temperature, F.	Pulse	Respiration
7552	Pernicious anemia; chronic type; duration, July, 1915 to November, 1917; no remissions	♂	53	11/15/17	164.1	59.9	98.6	70	9.8
				700 c.c. washed R.B.C. in physiol. saline	11/16/17					
				600 c.c. washed R.B.C. in physiol. saline	11/18/17					
				11/19/17	60.3	98.4	66	12.1
				550 c.c. washed R.B.C. in physiol. saline	11/21/17					
8448	Pernicious anemia; chronic type; duration, April, 1917 to April, 1918; yellow pallor of skin noticed first April, 1918; no remissions	♀	62	12/ 5/17		59.7	97.8	60	10.6
				4/15/18	158.6	49.1	98.8	65	9.3
				900 c.c. washed R.B.C. in physiol. saline	4/16/18				80	14.9
				4/17/18	48.5	98.0	73	18.5
				900 c.c. washed R.B.C. in physiol. saline	4/18/18					
7739	Pernicious anemia; chronic type; arteriosclerosis; ventral hernia; duration, February, 1916 to March, 1918; remission September, 1917 to November, 1917	♀	59	4/20/18	48.6	98.0	68	15.9
				800 c.c. washed R.B.C. in physiol. saline	4/29/18	50.8	98.2	72	13.8
				4/30/18	49.3	99.2	70	13.0
				12/26/17	155.9	41.8	99.4	72	13.7
				600 c.c. washed R.B.C. in physiol. saline	1/ 6/18					
8204	Secondary anemia (brief duration); menorrhagia; duration of anemia, September, 1917 to March, 1918	♀	35	1/ 9/18	40.8	99.0	85	13.2
				1/16/18	39.3	99.2	80	14.0
				2/ 7/18	41.3	99.0	79	13.3
				150 c.c. plasma and platelets.....	2/24/18					
				700 c.c. washed R.B.C. in physiol. saline	2/25/18	39.9	99.6	87	13.8
8217	Pernicious anemia; acute type; duration of anemia, February, 1918 to March, 1918; no remissions	♀	56	2/26/18	40.2	98.4	72	12.4
				700 c.c. washed R.B.C. in physiol. saline	2/28/18	40.1	98.6	74	12.9
				135 c.c. plasma and platelets.....	3/ 1/18					
				3/ 5/18	40.6	98.6	66	13.6
				750 c.c. washed R.B.C. in physiol. saline	3/ 7/18	164.7	39.5	99.2	102	18.4
8040	Pernicious anemia; chronic type; febrile and dangerously ill at present; anemia first noted June, 1916; complete remission January, 1917 to August, 1917; gradual decline August, 1917 to February, 1918; death, May, 1918	♀	29	3/21/18	39.0	99.4	84	16.3
				3/25/18	39.1	98.4	67	16.1
				3/ 8/18	170.6	59.7	100.0	101	22.1
				950 c.c. washed R.B.C. in physiol. saline	3/10/18					
				900 c.c. washed R.B.C. in physiol. saline	3/12/18					
8337	♀	29	500 c.c. washed R.B.C. in physiol. saline	3/14/18					
				3/15/18	61.8	98.6	77	24.6
				900 c.c. washed R.B.C. in physiol. saline	3/19/18					
				3/20/18	61.7	98.6	77	23.7
				3/25/18	60.9	98.6	83	21.7
8040	♀	29	450 c.c. washed R.B.C. in physiol. saline	4/ 2/18	59.4	98.8	80	20.6
				450 c.c. washed R.B.C. in physiol. saline	4/ 4/18					
				4/ 5/18	59.5	97.6	74	20.1
				4/ 9/18	59.9	98.6	78	20.1
				800 c.c. washed R.B.C. in physiol. saline	2/10/18	150.1	40.7	102.8	118	17.8
8337	♀	29	825 c.c. washed R.B.C. in physiol. saline	2/13/18					
				675 c.c. citrated whole blood.....	2/15/18					
				2/16/18	40.0	97.8	55	13.6
				3/26/18	39.4	100.6	102	14.2
				800 c.c. washed R.B.C. in physiol. saline	3/29/18					
8337	♀	29	3/30/18	39.6	98.8	79	14.0
			

The two periods disagreed by 6 per cent.
The two periods disagreed by 4 per cent.
The two periods disagreed by 5 per cent.
The two periods disagreed by 4 per cent.

DISCUSSION OF RESULTS

A survey of Table 1—the data on the untreated cases—reveals the same irregularities found throughout the literature. The metabolism falls in part within normal limits, in part above and below

normal. It is parallel neither with the marrow activity as represented by the blood picture, history and general condition of the patient, nor

—TREATMENT IN SIX CASES OF ANEMIA

Metabolism						Blood Picture							Remarks
Volume per Minute, L.	Volume per Respiration, C.c.	Oxygen Consumption per Minute, C.c.	Respiratory Quotient	Total Calories per Hour	Per Cent. Divergence from Aver. Normal Basal Linear	Date	Hemoglobin, per Cent.	R. B. C., Million	W. B. C.	Nucleated R. C.	Anisocytosis	Poikilocytosis	
4.02	410	186	0.75	52.7	-15	11/13/17	87	3.2	8,400	0	++	+	Plates decreased. Many macrocytes Many macrocytes
3.93	327	179	0.81	51.6	-17	11/18/17	96	4.0	8,500	0	++	+	
						11/26/17	104	4.5	5,400	0	++	0	
3.62	344	161	0.80	46.2	-26	12/ 5/17	83	5.4	6,200	8	+	0	Eight normoblasts
3.60	388	161	0.78	45.9	-26								
4.56	307	159	0.75	45.1	-11								
5.12	277	163	0.72	45.8	- 8	4/15/18	30	1.0	5,000	0	++	+	One myelocyte seen on this date One normoblast, one megakaryoblast seen Rare stippled cells present Four myelocytes seen
4.48	283	152	0.75	43.3	-14	4/17/18	55	1.9	2,400	0	0	0	
4.38	319	153	0.85	44.6	-13	4/20/18	90	3.4	3,800	2	0	0	
4.13	318	148	0.84	43.1	-14*	4/29/18	75	3.2	3,200	0	0	0	
4.50	329	182	0.76	51.8	+ 9†	4/30/18	75	3.3	3,300	1	0	0	
3.93	298	170	0.76	48.4	+ 3‡	12/29/17	40	1.2	6,600	1	+	++	One myelocyte, one normoblast
3.60	258	155	0.72	43.6	- 7	1/ 7/18	44	2.1	4,000	0	+	+	Marked stippling
3.99	301	166	0.76	47.1	- 2	1/14/18	45	2.2	5,300	0	+	+	
						2/ 6/18	60	2.4	8,200	0	+	0	
						2/26/18	53	2.2	3,400	0	0	+	Polychromatophilia constant in this patient
4.16	302	168	0.75	47.8	+ 2								
4.25	344	169	0.77	48.3	+ 3‡								
4.20	325	156	0.78	44.5	- 5								
3.95	290	149	0.81	42.9	- 9								
5.11	278	193	0.74	56.2	+11								
4.88	300	183	0.79	52.4	+ 4	3/ 6/18	30	2.2	3,800	0	+	+	Plate count, March 3, 251,000
4.19	260	160	0.78	45.7	-10	3/20/18	46	4.2	7,800	0	0	+	Many macrocytes
						3/25/18	74	4.9	5,600	0	+	+	Few polychromatophills, stippled cells present
6.55	297	241	0.73	68.0	+15	3/ 7/18	25	0.8	2,500	1	++	++	One megakaryoblast. Polychromatophilia slight
						3/15/18	64	2.4	1,800	0	++	++	Macrocytes numerous Macrocytes numerous Macrocytes numerous
						3/22/18	70	2.8	3,100	1	++	++	
						3/25/18	70	3.2	2,400	0	+	+	
6.52	266	216	0.79	62.0	+ 3	4/ 1/18	64	3.1	2,900	0	+	+	Macrocytes numerous
6.12	256	213	0.77	60.7	+ 1	4/ 5/18	75	3.5	4,800	0	+	+	No polychromatophilla nor stippling
5.72	264	212	0.80	61.0	+ 2	4/ 9/18	95	4.0	4,200	0	+	+	No polychromatophilla nor stippling
5.89	286	225	0.79	64.6	+10								
5.77	287	217	0.81	62.8	+ 6								
5.51	275	213	0.80	61.3	+ 3‡								
5.50	309	205	0.75	58.1	+20	2/ 8/18	55	2.1	3,200	0	+	+	Achromia marked
						2/16/18	...	4.5	2,400	0	+	+	One megakaryoblast seen Polychromatophilla not pronounced in this
						3/25/18	55	...	2,500	1	0	+	
						3/30/18	65	...	1,800	0	0	+	
3.67	271	153	0.74	43.2	-10‡								
4.18	294	181	0.78	51.9	+ 9								
4.05	290	167	0.76	47.6	- 1‡								

† The two periods disagreed by 4 per cent.

‡ The two periods disagreed by 4 per cent.

‡ The two periods disagreed by 7 per cent.

with the immediate gravity of the case. Indeed, with the exception of Numbers 4, 9 and 12, the most severe cases were those who showed a metabolism beyond normal limits in either direction. In general, these severe types followed the order that the long standing, chronic cases gave a diminished, and the recent more acute ones, an elevated metab-

olism. It should be noted, however, that of those with a calorific output above normal, two patients (Numbers 15 and 18) had distinctly elevated temperatures, which would suggest that the increased metabolism was attributable, in part at least, to some influence other than the anemia. Two others (Numbers 16 and 17) of those with an increased energy output showed complications in the larger organs. Besides this coincidence between the intensity of metabolism and the duration of the disease, there is a certain parallelism to be seen between

TABLE 3.—ADMISSION AND END DATA ON—

O. C.	Med. No.	Diagnosis	Sex	Age	Treatment	Dates Metabolism and Treatment	Metabolism				
					Description		Height, Cm.	Weight, Kg.	Buccal Temperature, F.	Pulse	Respiration
T.	7793 8298	Pernicious anemia; chronic type; duration, August, 1916 to January, 1918; remission, September, 1917 to November, 1917	♂	46	700 c.c. washed R.B.O. in physiol. saline 700 c.c. washed R.B.O. in physiol. saline 700 c.c. washed R.B.O. in physiol. saline	1/ 4/18 1/ 8/18 3/16/18 3/17/18 3/18/18	173.2	70.7	98.6	67	93
S.	7470 7669*	Splenic anemia; splenomegaly; duration of anemia, October, 1916 to October, 1917; progressing slowly and without remission	♀	18	Splenectomy.....	11/10/17 11/13/17 12/11/17	160.2	68.5 48.3	98.0 98.6	71 61	107 191
S.	7434	Pernicious anemia; lateral sclerosis; chronic type; duration of anemia, July, 1916 to October, 1917; no remissions	♀	40	250 c.c. eltrated whole blood.....	10/26/17 10/31/17	157.5	56.6	98.2	69	136
C.	7951	Secondary anemia; hemophilia; had had many attacks of bleeding but was well and at heavy work before the present hemorrhage	♂	52	650 c.c. eltrated whole blood.....	1/15/18 2/ 6/18	178.8	66.7	98.2	63	110
W.	8562	Pernicious anemia; chronic type; duration, January, 1917 to April, 1918; no remissions	♂	58	900 c.c. washed R.B.O. in physiol. saline	4/25/18 4/26/18	184.4	63.5	98.0	65	111
O.	7527	Secondary anemia; pericarditis; pleurisy; peritonsillar abscess; duration of anemia about eight months	♂	39	550 c.c. washed R.B.O. in physiol. saline	1/ 5/18 1/ 8/18	172.2	53.1	99.2	78	135
C.	7400	Splenic anemia; splenomegaly; duration of anemia, September, 1917 to October, 1917	♀	60	117 millieuries radium applied to spleen 24 hours	10/23/17 10/28/17 10/30/17	157.0	56.6 55.8	98.8 99.2	97 90	146 145

Surgical number.

pulse and metabolism. The abnormality of the metabolism, however, is far more marked than that of the pulse.

Tables 2 and 3, in contrast to Table 1, present a decidedly consistent picture. Most striking is the effect found as the result of treatment in all except three cases (Numbers 2, 3 and 16). Not only did the metabolism invariably fall, but, with the exception of Case 15, it reached a level either on the lower limit of or below normal. And this new level tended to hold despite further transfusions, and to repeat itself when a similar course of treatment was instituted in any later relapse. Parallel with this diminution in metabolism was a drop

in the pulse, in the respiratory activity as represented by the minute volume, and in the temperature if it had previously been elevated. The respiratory quotient was higher and, as was natural after transfusion, the simple cell count and the percentage hemoglobin were increased.

Of these changes following on treatment, the metabolism alone was of slow response. While the pulse and respiratory activity, the temperature and the blood picture reacted at once, or at least within

—CASES STUDIED DURING TREATMENT

Metabolism						Blood Picture							Remarks
Volume per Minute, L.	Volume per Respiration, C.c.	Oxygen Consumption per Minute, C.c.	Respiratory Quotient	Total Calories per Hour	Per Cent. Divergence from Aver. Normal Basal Linear	Date	Hemoglobin, per Cent.	R. B. C., Million	W. B. C.	Nucleated R. C.	Anisocytosis	Poikilocytosis	
4.31	463	215	0.78	61.5	-13	1/ 3/18	69	2.3	6,000	0	++	++	Few polychromatophilic and stippled cells. Many macrocytes. No stippling.
						3/18/18	55	2.3	4,800	0	++	0	
4.94	460	208	0.80	60.0	-15	11/ 8/17	68	3.0	4,800	0	0	0	Slight achromia
5.22	281	209	0.73	59.1	+ 5	12/ 8/17	75	4.4	12,000	0	0	0	
4.55	222	159	0.88	46.5	-15†								
4.15	307	172	0.75	48.7	-14	10/29/17	68	2.2	4,200	0	+	+	Moderate polychromatophilia on Oct. 24, 1917
5.52	501	210	0.84	61.1	-12	2/ 7/18	55	2.8	5,400	0	+	+	Marked achromia
5.59	397	228	0.76	65.1	- 6	4/26/18	90	3.0	2,300	0	+	+	
4.92	364	225	0.71	63.2	- 2	1/ 5/18	53	1.9	10,000	0	+	+	A case of chronic sepsis with constant slight rising rise in temperature
5.42	376	217	0.75	61.5	+15†	10/22/17	68	3.6	7,000	0	+	+	Moderate polychromatophilia
5.38	372	212	0.76	60.4	+15								

† The two periods disagreed by 4 per cent.
‡ The two periods disagreed by 6 per cent.

twelve hours, the maximum effect on the metabolism seemed to take place only after a few days.

A discussion of the six cases reported in Table 2 will best show the facts as summarized in the foregoing.

Case 1 is of peculiar interest as representing chronic pernicious anemia of long duration. A hospital report shows this patient to have had a metabolism of minus 7 per cent. in 1916 (a year prior to the determination we have recorded). While his pulse and minute volume diminished soon after transfusion, it was not until some days later

that his heat output showed any change. It then seemed to have reached the true and remarkably low level at which it held.

Case 3 was likewise one of chronic anemia. This patient, however, as noted before, showed no metabolic response to transfusion. Her pulse, respiratory activity and respiratory quotient reacted in the general way, as did also her subjective symptoms. Of the last, the increased power to take food is especially worthy of mention. It may possibly be that this improved absorption of nutriment on the part of a person who had been using a decidedly subnormal amount of food masked what would otherwise have shown as a decreased metabolism.

Case 12, also one of long standing anemia, was carried through two periods of transfusion and moderate improvement, with an intervening relapse. Here the pulse rose after the first transfusion, but later pulse, metabolism, and respiration showed the usual diminution. At the end of each course of treatment the basal heat output showed the same level. Here, as in Case 1, this metabolic response to transfusion occurred only after a few days (compare the determinations of January 9 and 16, and of February 26 and 28), while the pulse and respiration dropped within twelve hours.

Case 14, under spontaneous improvement in a secondary anemia, showed the same type of changes, even to the blood picture, as occurred in all the cases after transfusion. Transfusion in this instance merely hastened the normal process of regeneration. In other words, natural improvement of the blood composition in anemia, as well as artificial improvement by transfusion, at first suppresses the stimulus acting on the body cells. This seems true no matter what the initial metabolism.

Case 15 represents a type diametrically opposite to Case 1. The onset of the disease was recent, the temperature before treatment was high, the metabolism and pulse elevated, the subjective symptoms grave. The response to transfusion, both metabolically and symptomatically, was marked, but of comparatively short duration. The cause of the disease was active, and the original symptoms soon reappeared, to subside once again to the same level as after the first series of transfusions. Even here, in an acute febrile case, responding to transfusion almost instantaneously in all other ways, the pronounced effect on the metabolism occurred only after an interval of a few days. (Compare date of April 5 and 9.) Likewise transfusion beyond a certain point had no effect on the energy requirement. (Compare the date of March 15, 20 and 25.)

What was stated for Case 15 may be practically repeated for Case 18. The patient here was dangerously ill and in the terminal stage of the disease. The metabolic level of the former was slightly lower, but otherwise the two patients presented very similar symptoms and reactions.

From the fact that the metabolism always falls after transfusion, no matter what its initial relation to normality, that this drop is preceded over a considerable interval of time by a fall in the pulse and respiratory activity, that the energy output seems to find a constant level beyond which it shows no further diminution, and that this level is either below or on the lower limit of normal — from these facts we feel that *two opposing factors, outside of any muscular activity, exert an influence on the metabolism of the anemic individual.*

First, there is a stimulus to the cells — perhaps only to certain ones such as those of the blood producing organs. The extent of this stimulus is expressed in the diminution of the metabolism which follows on transfusion. It is lost slowly as the cells readjust themselves to blood of more normal composition. Hence, the time interval between the introduction of blood into the body and the energy response of the organism.

Secondly, there is the opposing factor to the increased metabolism — namely, the tissue alterations attendant on the disease. The pathologic result of any anemia, and particularly of pernicious anemia, is replacement of normally active tissue by fat and water. In chronic pernicious anemia this replacement may reach an extreme degree, and expresses itself by the diminished heat output found in typical chronic cases and by the apparent tendency of all the cases to show a low metabolic level after transfusion when the stimulating factor has subsided.

The amount by which the metabolism falls after transfusion shows the strength of the stimulus exerted on the body cells, possibly for the purpose of blood production. And the level to which the metabolism falls shows the true bodily condition of the patient. A chronic case may thus be expected to reveal a decidedly lowered energy output, while from a recent case, where tissue compensation had not yet become an active factor, one may look for a practically normal calorific requirement. In our opinion, transfusion is a measure by which early cases of pernicious anemia may be assisted toward a remission and may be saved some degree of the fatty replacement of active tissue which in the end reduces them to a condition of sluggishness somewhat comparable to that seen in myxedema. If the case simply has a long history, the whole story is not told, since what is of importance is the length of the anemic periods and the possibility for bodily change which they present.

As a result of the work we have reported our course of action is now as follows: A typical case of pernicious anemia is admitted to the ward. After several days rest in bed, if food is being taken well

and if the temperature has become normal, a metabolism determination is carried out. Let us suppose the result is minus 10. In such an instance transfusion may result in a certain amount of immediate comfort, but there is little probability it will do more. The case is a chronic one in terms of the patient's actual physiologic condition. If the result is plus 10, transfusion is worth while. Such a result, a plus determination, will be given in persistently febrile cases on the first trial, and if as a consequence of transfusion the fever disappears and subsequent determinations give a pronounced minus value, again we can feel that further transfusion holds little in store. On the other hand, if the reduction in metabolism does not fall below normal either as a result of rest in bed or the first transfusion, the individual is one who has not progressed far in the disease, and transfusions should be pushed. While a course of transfusions does not prevent the development and progress of neurologic lesions, it does postpone the muscular sluggishness, which eventually reduces the chronic case of pernicious anemia to the state of a helpless burden.

CONCLUSIONS

1. Transfusion in cases of anemia produced the following results:
 - a. a diminution of metabolism;
 - b. a diminution of pulse and respiratory activity;
 - c. a drop in temperature if it had previously been elevated;
 - d. a rise in percentage hemoglobin and in the simple blood count.
2. The response of the metabolism to transfusion lags behind that of all the other factors by an interval of several days.
3. The lowering of metabolism is, therefore, not due simply to a cessation of the compensatory muscular activity of the anemic individual.
4. Before treatment the metabolism may be within normal limits or it may be above or below normal.
5. After transfusion the metabolism always reaches a normal or diminished level.

These facts suggest that the metabolism of the anemic individual is dependent on two contending factors, outside of any effects from compensatory muscular activity.

1. In untreated acute cases there is evidently some type of stimulation to the body cells in general and the amount of this stimulation is represented by the fall in metabolism after transfusion.

2. There are coincident progressive tissue alterations which tend to reduce metabolism. These alterations are represented by the diminished metabolism of the chronic cases, and by the low level to which the metabolism falls in practically all cases as a result of transfusion.

STUDIES ON ALIMENTARY HYPERGLYCEMIA AND GLYCOSURIA *

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In 1647 Thomas Willis recognized the presence of sugar by its sweet taste in the urine of diabetics. This sugar was identified as glucose by Chevreul in 1815. That diabetic blood also contained sugar was first recognized by Dobson in 1775, and his observation was confirmed the following year by Cullen.¹

In 1831 Tiedemann and Gmelin² showed that sugar was normally present in the blood after meals, and that it originated in the digestion of starchy food in the intestine. Up to this time sugar had been considered a pathologic product in the blood and urine of diabetics. The fact that sugar is present in the blood of an animal on a carbohydrate-free diet was first demonstrated by Claude Bernard in 1848. Eight years later, Chauveau asserted that sugar was a constant constituent of the blood, that its presence was not dependent on the diet, and that in the fasting state the sugar value remained constant. The dependence of glycosuria on hyperglycemia was recognized at this time following the work of MacGregor, Rollo and Ambrosini, and tests for the assimilation limit for glucose and starch were instituted by C. Schmidt, v. Becker, Schiff, Lehmann, Frerichs and others, the urine being tested for sugar. This assimilation-limit for glucose has been found to be not at all constant, varying in different individuals and in the same individual, being greatly lowered by starvation as shown by Hofmeister.³ The method usually employed was to give from 50 to 200 gm. of glucose to an individual of average weight, and to test the urine at intervals for the presence of sugar. The normal values given by different authors vary from 50 to 200 gm. In many cases the urine was examined at intervals varying from one to twenty-four hours after the ingestion of the sugar, and this, with inaccurate methods of sugar determination, largely explains the discrepancies. Other sources of error are the state of health, nutrition and body weight of the patient. The advent of practical methods of blood analysis directed the attention of investigators to tests of alimentary hyperglycemia and the determination of the patient's toler-

* From the Laboratory of Pathological Chemistry, and the Department of Medicine, New York Post Graduate Medical School and Hospital.

1. Bernard, Claude: *Compt. rend de l'acad. d. sc.*, 1876, p. 1405

2. Tiedemann and Gmelin: *Die Verdaung nach Versuchen*, Heidelberg, 1831.

3. Hofmeister: *Arch. f. exper. Path. u. Pharmacol.* 26:355, 1891.

ance for glucose in this way. Results of such tests have been published by Liefmann and Stern,⁴ Boudouin,⁵ Frank,⁶ Wacker,⁷ Tachau,⁸ Jacobson,⁹ Bergmark,¹⁰ Hopkins,¹¹ Cummings and Piness,¹² Hamman and Hirschman,¹³ Denis and Aub¹⁴ and others. In many of these tests the estimations were made one and two hours after the ingestion of glucose, and the results compared with the preformed sugar value. In other cases the test was more elaborate, the blood being examined at frequent intervals for a period of from four to six hours. These observers seem to agree that in a normal person, following the ingestion of sugar, the blood sugar reaches its greatest concentration in from one-half to one hour, and that the normal value is again reached

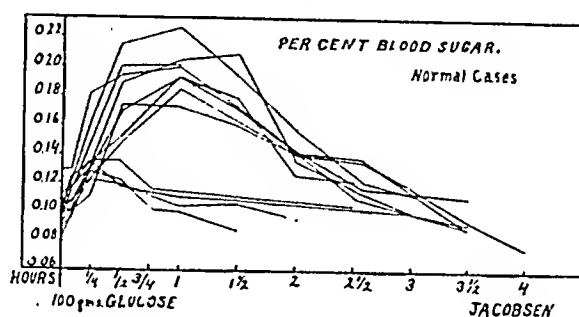


Chart 1

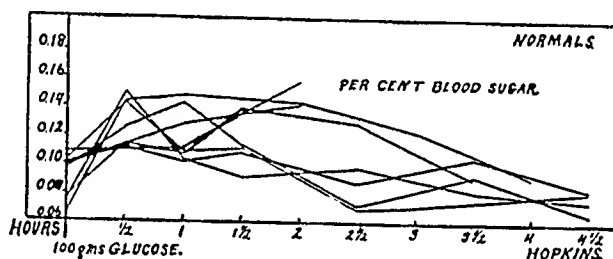


Chart 2

in from two to three hours' time. There is no agreement as to the height of the hyperglycemia. Great variations are to be expected. Aside from the inaccuracies of the various methods we have the uncertain factors of intestinal absorption, state of nutrition, weight of the subject, glycogenetic and glycolytic powers, renal permeability, and glycolysis in the intestine and in the withdrawn blood before the test

4. Liefmann and Stern: *Biochem. Ztschr.* **1**:299, 1906.
5. Boudouin: *Thèse de Paris*, 1908.
6. Frank: *Ztschr. f. physiol. Chem.* **70**:291, 1910.
7. Wacker: *Ztschr. f. physiol. Chem.* **67**:197, 1910.
8. Tachau: *Arch. f. klin. Med.* **104**:437, 1911.
9. Jacobsen: *Biochem. Ztschr.* **56**:471, 1913.
10. Bergmark: *Jahrb. f. Kinderh.* **80**:373, 1914.
11. Hopkins, A. H.: *Am. J. M. Sc.* **149**:254, 1915.
12. Cumings and Piness: *Arch. Int. Med.* **19**:777, 1917.
13. Hamman and Hirschman: *Arch. Int. Med.* **20**:761, 1917.
14. Denis and Aub: *Arch. Int. Med.* **20**:964, 1917.

is carried out. Illustrating these agreements and variations, composite charts (Charts 1, 2 and 3) made from figures published by Jacobsen,⁹ Hopkins,¹¹ and Hamman and Hirschman¹² are given.

A combination of blood and urine analyses following the ingestion of glucose has been found more instructive. In the fourteen normal cases reported by Jacobsen⁹ (Chart 1) sugar was found in the urine in all those whose blood sugar reached a value of 0.174 per cent.; in those below 0.16 per cent. sugar was not found in the urine. Jacobsen's work shows the fallacy of blood analyses at one-hour intervals, as in many normal cases following the ingestion of 100 gm. of glucose, hyperglycemia had already passed off by the end of the first hour.

Bailey¹⁵ reported a normal case on whom frequent blood and urine sugar tests were made following the ingestion of 75 gm. of glucose. The type of blood sugar curve was similar to those of Jacobsen⁹ and, as in his cases, the kidneys actively excreted sugar after a concentration of 0.167 per cent. had been reached in the blood.

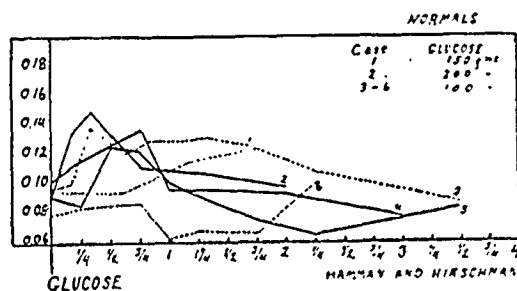


Chart 3

Hamman and Hirschman¹² carried out similar tests on six normal persons, using from 100 to 200 gm. of glucose. In three of their cases the blood sugar curve was of a similar type to those of Jacobsen; the others were very irregular (Chart 3). In these cases active renal excretion of sugar began at blood sugar concentrations varying from 0.124 to 0.255 per cent., giving an average of 0.17 per cent.

An important observation on all of these tests is the marked disproportion between the greatest blood sugar concentration and the amount of sugar ingested, allowances being made for differences in body weight. This disproportion is seen in the work of individual authors and makes one think that sugar tolerance tests based on blood sugar estimations are really tests of intestinal absorption.

15. Bailey, C. V.: *Proc. Soc. Exper. Biol and Med.* **13**:153, 1916.

TESTS OF ALIMENTARY HYPERGLYCEMIA AND GLYCOSURIA

Stimulated by the works of Bang,¹⁶ Jacobsen,⁹ and Hopkins,¹¹ the present work was undertaken in an attempt to show the relation of glycosuria to hyperglycemia as found in health and as influenced by disease. It was hoped that in such tests interesting observations could be made on variations in blood volume, on the rate of sugar increase in corpuscles as compared to that in the plasma, and on the influence of urine excretion on glycosuria.

METHOD OF PROCEDURE

The subjects partook of a light meal at 5:30 on the afternoon preceding the tests. On the following morning the experiment was begun before anything had been eaten or drunk. The bladder was emptied and later a specimen of urine was passed on which was determined the rate of urinary excretion and the presence or absence of sugar. A specimen of blood was obtained at this time by venipuncture. Following this a certain amount of glucose in a known volume of weak tea was given by mouth and blood and urine specimens obtained at frequent intervals for a period of six or seven hours. In some cases fluid was given during this period. The subject was kept quiet in a reclining posture throughout. Urine sugar tests were made qualitatively by Benedict's method;¹⁷ quantitatively by Benedict's or Myers'¹⁸ methods and by means of the polariscope. In some cases the sugar was determined to be glucose by the character of its osazone.

Blood sugar was estimated by a modification of the Lewis and Benedict¹⁹ method.

Hemoglobin tests were made with the Hellige colorimeter.

Plasma volume was determined by centrifuging the blood in graduated tubes. Chlorids in the urine were estimated by the Volhard-Harvey method. Sugar estimations were made on unwashed corpuscles from which the plasma and upper layers of cells had been pipetted off leaving a known volume of cells in the centrifuge tube.

The data from these last estimations unfortunately do not give one a correct idea of the relative glucose increase in corpuscles and plasma, as by this method a half hour elapsed before the plasma and corpuscles were separated. This gave time for absorption by the corpuscles and a more even distribution of the glucose. The data are, however, of value in showing the distribution of glucose in blood, in which the glucose concentration is not changing. Gradwohl and Blavis,²⁰ who, by the way, were student and technician, respectively, in the laboratory where this work was being done, have published results similar to these now reported.

16. Bang, I.: *Der Blutzucker*, Wiesbaden, 1913.

17. Benedict, S. R.: *J. Biol. Chem.* 5:485, 1909; 9:57, 1911.

18. Myers, V. C.: *Proc. Soc. Exper. Biol. and Med.* 13:178, 1916.

19. Myers, V. C., and Bailey, C. V.: *J. Biol. Chem.* 24:147, 1915.

20. Gradwohl and Blavis: *J. Lab. & Clin. M.* 2:416, 1916-1917.

Alimentary Glucose Test in a Normal Person

CASE 1.—S. S., male, aged 18, was admitted to hospital for observation as a suspected case of pulmonary tuberculosis. Aside from being poorly nourished, nothing abnormal was found on physical examination. His morning blood sugar on two occasions was 0.1 and 0.11 per cent. On the morning of May 15, 1916, he was tested with 75 gm. of glucose. The results are shown in Chart 4 and Table 1. The patient was quite nervous at the beginning of the test, and this probably accounts for the preformed sugar being higher than on previous occasions. The urine sugar was slightly lower than the synchronous blood sugar. Following the administration of the glucose, the blood and urine sugar increased at the same rate up to a concentration of 0.167 per cent., when the urine sugar increased rapidly to 0.89 per cent., although the blood sugar at this time had reached only 0.22 per cent. The blood sugar curve is of the same type as found in normals by Jacobsen and others. The urine sugar value returned to normal more slowly than the blood sugar. Following the ingestion of glucose the blood volume (as shown by the estimation of hemoglobin) increased 7 per cent. during the first half hour, returning to normal in one and one-half hours, although the blood sugar at this time was concentrated. Epstein²¹ has frequently referred to this volume increase. The rate of urinary excretion decreased notwithstanding the fact that 400 c.c. of fluid were taken with the glucose. Not before the blood sugar had reached its highest level and was on the decline, did the rate of urinary excretion increase.

TABLE 1 (CASE 1, S. S., 5/15/16).—ALIMENTARY GLUCOSE TEST IN A NORMAL PERSON

Time		Blood						Urine			Field Intake, C.c.
		Hemo-globin, Units	Plas-ma, per Cent.	Sugar			C.c. per Hour	Sugar		Bene-dict's Meth-od, Quali-tative	
				In Whole Blood, per Cent.	In Plasma, per Cent.	In Cor-puscles, per Cent.		Myers Method			
								Per Cent.	Gm. per Hour		
A. M.	Hr.										
9:10	...	80	45.5	0.12	0.118	0.121	36.0	0.020	0.025	0	
9:15	75 gm. glucose			
9:30	1/4	77	44.5	0.153	0.127	0.132	28.2	0.171	0.015	0	
9:50	1/2+	73	46.3	0.172	0.19	0.154					
10:10											
10:15	1	77	46.0	0.22	0.225	0.193	31.2	0.591	0.28	+++	
10:40	1 1/2-	80	45.3	0.216	0.22	0.211					
11:00											
11:15	2	78	47.0	0.158	0.147	0.147	31.8	0.405	0.129	+++	
11:30											
11:45	2 1/2	79	46.0	0.147	0.147	0.147	16.8	0.315	0.053	++	
12:00 M.											
P. M.											
12:15	3	78	47.0	0.134	0.113	0.124	22.8	0.27	0.06	+	
1:00	3 3/4	78	46.5	0.135	0.121	0.124					
1:45	4 1/2	76	45.5	0.129	0.121	0.113	21.0	0.252	0.032	+	
2:00											
2:15	5	77	42.0	0.129	0.126	0.113	22.8	0.162	0.037	0	
3:15	6	78	40.0	0.087	0.085	0.091					

This experiment seems to indicate that a normal person, when uninfluenced by food or fluid intake, has reducing substances present in equal concentration in both blood and urine. Following the inges-

21. Epstein, A. A.: Studies on Hyperglycemia in Relation to Glycosuria. New York, 1916.

S.S. 15-V-16

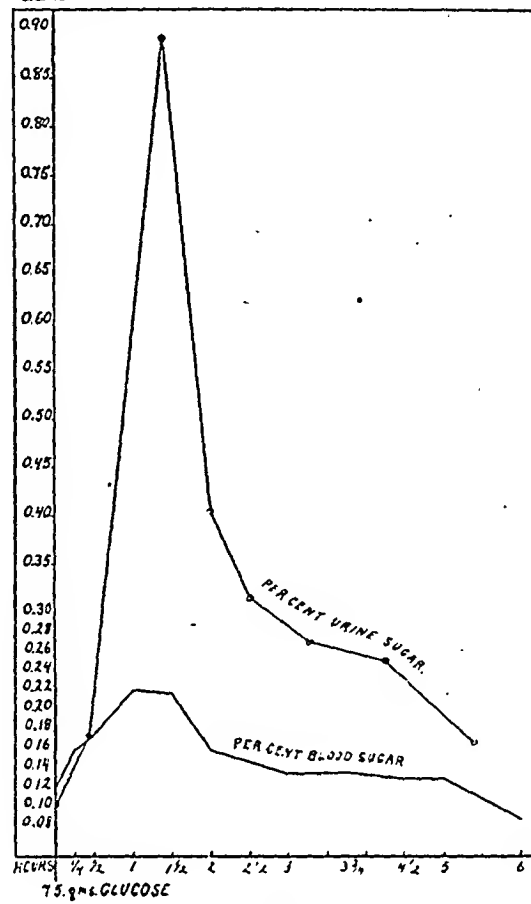


Chart 4

M.B. 11-VIII-15

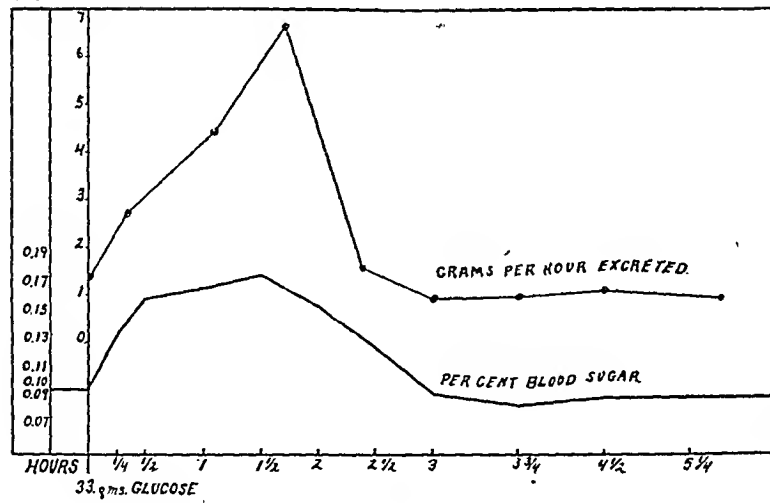


Chart 5

tion of glucose, urine sugar parallels that of the blood up to the latter's concentration of 0.16 to 0.17 per cent. As the blood sugar increases beyond this point the kidneys actively excrete sugar. This excessive excretion decreases as the hyperglycemia passes off. There seems to be an attempt to control the blood sugar concentration by an increase in blood volume. This is partly brought about by a decrease in urinary excretion.

A comparison of the hyperglycemic curves in plasma and corpuscles indicates a more rapid rise in plasma than corpuscles. (This difference, however, is probably much greater than the figures show. As before stated, a half hour elapsed before plasma and corpuscles were separated, giving time for an even distribution of the glucose.)

The findings in this case emphasize the necessity of adopting Benedict's term "glycuresis"²² to indicate active excretion of sugar in contradistinction to the amount found in the urine during the fasting state.

TABLE 2 (CASE 2, M. B., 8/11/15).—ALIMENTARY GLUCOSE TEST IN A CASE OF RENAL DIABETES

Time		Blood Sugar, per Cent.	Urine				Fluid Intake, C.c.
A. M.	Hr.		C.c. per Hour	Chlorids, Gm. per Hour	Sugar		
					Per Cent.	Gm. per Hour	
9:15	...	0.093	60.0	0.046	3.12	2.0	225
9:45	33 gm. glucose	44.0	2.94	1.22	
10:00	1/4	0.135	
10:20	1/2	0.159	58.0	0.1056	4.63	2.83	225
10:30							225
10:45	1	0.168	
11:00	1 1/4	0.172	66.0	0.145	6.66	4.596	
11:10							225
11:15	1 1/2	0.176	
11:45	2	0.156	97.0	0.218	6.75	6.7	
P. M.							225
12:15	2 1/2	0.105	
12:25			159.0	0.254	1.04	1.65	
12:45	3	0.093	94.0	0.169	0.952	0.897	225
1:00	3 1/2	0.086	
1:25	4	0.088	150.0	0.21	0.657	0.956	
1:45							225
2:00	4 1/2	0.092	
2:15			90.0	0.14	1.2190	1.097	
3:00	5 1/4	0.092	225
3:45	6	0.092	84.0	0.134	1.086	0.912	

*Alimentary Glucose Test in a Case of "Renal Diabetes"*²³

CASE 2.—M. B., female, aged 31, had persistent glycosuria for at least ten years, resisting repeated attempts at treatment; no symptoms of diabetes. For many years her only complaint had been lack of reserve energy. Restriction of diet caused extreme weakness and rapid loss of weight. Her urine showed

22. Benedict, S. R., and Osterberg, E.: J. Biol. Chem., 34:258, 1918.
23. For further discussion of renal diabetes see Bailey, C. N.: Am. J. M. Sc. 157:221, 1919.

a trace of protein and a few hyaline and granular casts. Blood pressure: systolic, 110; diastolic, 65.

On the morning of Aug. 5, 1915, her blood sugar was 0.09 per cent., the synchronous urine sugar being 1 per cent. Two days later, with a blood sugar of 0.11 per cent., the urine contained 1.6 per cent. sugar. August 11, she was tested with 33 gm. of glucose. The results are shown in Chart 5 and Table 2. (At this time the patient was four months' pregnant.)

One sees that the patient excreted sugar at the rate of 2 gm. per hour, although at this time her blood sugar was normal. The blood sugar curve is slightly delayed and prolonged. The excretion of sugar was excessive throughout. This being most marked at the 1½-hour period when sugar was being excreted at the rate of 6.7 gm. per hour, although the blood sugar was at about the concentration where normal kidneys become permeable.

The test was repeated fourteen months later. At this time the percentage of glucose in her daily urine had greatly increased, being 7.4 per cent. on Oct. 15, 1916, 6.94 per cent. on the 16th and 9.2 per cent. on the 17th. The glucose test was repeated October 13. The results are shown in Chart 6 and Table 3.

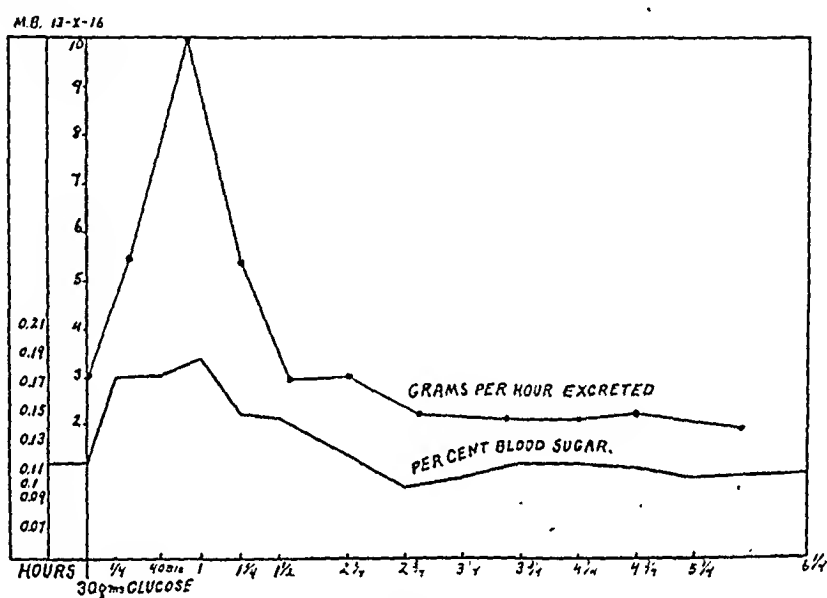


Chart 6

In this test the blood sugar value was within normal limits, but sugar was being excreted at 2.98 gm. per hour. The blood sugar curve is of the normal type. With a blood sugar of 0.189 per cent., sugar was being excreted at the rate of 9.9 gm. per hour. If we compare this test with the previous one (made when the patient was four months pregnant) we find that the blood sugar in the fasting state had increased in value. This, however, is explained by the first test having been made after three days' fasting, which lowers the value. The latter test was made after a ten-hour fast.

The excretory power of the kidneys had increased and the more rapid rise in blood sugar probably indicates an increased absorptive power of the intestines. In the first test the slight delay and prolongation of hyperglycemia is possibly due to slight embarrassment of the kidneys at that time.

In Table 3, the estimation of hemoglobin indicates a 6 per cent. increase in blood volume during the development of the hyperglycemia. The volume returned to normal with the blood sugar. The rate of urinary excretion fell off rapidly on the ingestion of glucose, notwithstanding the large fluid intake, and did not increase until the hyperglycemia had developed.

TABLE 3 (CASE 2, M. B., 10/13/16).—RESULTS OF SECOND GLUCOSE TEST

Time		Blood		Urine			Fluid Intake, Cc.
A. M.	Hr.	Hemo-globin, Units	Sugar, per Cent.	C.c. per Hour	Per Cent.	Gm. per Hour	
9:15	...	67	0.116	63.0	8.3	2.98	400
9:30	30 gm. glucose	
9:45	¼	62	0.177	36.0	11.9	5.25	
10:10	¾	61	0.177				
10:30	1	62	0.189	45.0	3.0	9.9	
10:40							
10:50	1¼	63	0.15	33.0	1.6	5.23	
11:00							
11:10	1¾	64	0.147	89.0	3.7	2.66	
11:30							
11:45	2¼	65	0.12	120.0	2.5	3.0	
12:00 M.							
P. M.							
12:15	2¾	65	0.10	37.0	6.2	2.31	
12:45	3¼	66	0.106				
1:15	3¾	67	0.116	56.0	5.6	2.69	
1:30							
1:45	4¼	67	0.114	36.0	6.0	2.19	
2:00							
2:15	4¾	67	0.112	31.0	6.5	2.21	
2:30							
2:45	5¼	68	0.106	28.0	6.8	1.9	
3:30							
3:45	6¼	68	0.108				

Alimentary Glucose Test in a Case of Early Mild Diabetes

CASE 3.—J. S. B., male, aged 42. Sugar was accidentally discovered in his urine during a routine military examination. He was apparently in excellent health, but had noticed slight polydipsia, polyuria and polyphagia. Sugar was constantly present in the daily urine, but hourly specimens showed that it was excreted only after meals. His morning blood sugar on several examinations was about 0.1 per cent. and at these times his urine was sugar-free.

March 3, 1916, he was tested with 60 gm. of glucose. The results are shown in Chart 7 and Table 4. (One hour before the test the patient negligently drank a cup of sweetened coffee which accounts for the high pre-formed blood sugar value.) The blood sugar curve rises a little more rapidly than normal, but otherwise is of the latter type. The excretion of sugar is excessive and follows the increase of blood sugar. At the 5½ and 6¼-hour periods one can determine that the kidneys actively excrete glucose between blood sugar concentrations of 0.123 and 0.126 per cent., which is much lower than normal.

On Jan. 24, 1917, the test was repeated, using 33 gm. of glucose. The results are shown in Chart 8 and Table 5. The blood sugar is of normal value. The blood sugar curve again rises and falls rapidly. Glucose excretion is excessive and appears at a lower blood sugar concentration than normal.

TABLE 4 (CASE 3, J. S. B., 3/3/16).—ALIMENTARY GLUCOSE TEST IN A CASE OF EARLY MILD DIABETES

Time		Blood					Urine					Fluid In-take. C.c.
		Hemo-globin, Units	Cells, per Cent.	Plas-ma, per Cent.	Sugar		C.c. per Hour	Sp. Gr.	Sugar		Chlor-ids, Gm. per Hour.	
					In Whole Blood, per Cent.	In Plasma, per Cent.			Per Cent.	Gm. per Hour		
A. M.	Hr.											
10:10	...	84.0	61	39	0.15	0.136	96.0	1.030	0.2	0.19	1.45	300
10:15	60	gm. glucose	
10:30	¼	82.0	61	39	0.205	0.192						
10:45	½	80.5	58	42	0.228	0.216	54.0	1.031	3.1	0.17	0.62	300
10:55												
11:00	¾	82.0	62	38	0.228	0.216	
11:15	1	83.0	63	37	0.216	0.204	84.0	1.033	5.3	4.45	0.7	
11:45	1½	82.0	62	38	0.185	0.156	78.0	1.035	4.6	3.59	0.81	
P. M.												
12:15	2	83.0	63	37	0.114	0.088						300
12:45	2½	83.0	65	35	0.09	0.068	31.8	1.029	1.0	0.318	0.48	
1:35	28.8	1.030	0.5	0.14	0.36	
1:45	3½	83.0	65	35	0.12	0.10	
2:45	4½	83.0	60	40	0.12	0.11	78.0	1.017	0.0	0.0	0.2	
3:00												
3:45	5½	84.0	63	37	0.126	0.116	36.0	1.023	0.25	0.09	0.17	
4:00												
4:30	6¼	83.0	63	37	0.123	0.112	26.4	1.030	0.0	0.0	0.2	
4:45												

TABLE 5 (CASE 3, J. S. B., 1/24/17).—RESULTS OF SECOND TEST

Time		Blood Sugar per Cent.	Urine				Fluid Intake, C.c.
			C.c. per Hour	Sp. Gr.	Sugar		
					Per Cent.	Gm. per Hour	
A. M.	Hr.						
9:45	...	0.104	44.4	1.023	0.0	0.0	400
10:00	33 gm. glucose	
10:15	$\frac{1}{4}$	0.141	34.2	1.022	0.71	0.24	
10:30	$\frac{1}{2}$	0.138					
10:40							
10:45	$\frac{3}{4}$	0.129					
11:00	1	0.108					
11:15	$1\frac{1}{4}$	0.114					
			24.0	1.030	1.66	0.398	
11:30	$1\frac{1}{2}$	0.104					
11:45	$1\frac{3}{4}$	0.09					
12:00 M.	2	0.10					
P. M.							
12:30	$2\frac{1}{2}$	0.098					
			18.0	1.031	0.3	0.054	
1:00	3	0.10					
1:30	$3\frac{1}{2}$	0.10					
2:30	$4\frac{1}{2}$	0.10	17.4	1.028	0.0	0.0	
3:00							

In these two tests the extent of the hyperglycemia seems to vary directly with the amount of sugar ingested.

In the first test the blood volume (as indicated by the hemoglobin) increased 3.5 per cent. during the increase in blood sugar, later returning to normal. Urinary excretion decreased following the ingestion of glucose.

Alimentary Glucose Test in a Case of Diabetes of Long Standing Without Kidney Involvement

CASE 4.—S. O., female, aged 65, had symptoms of diabetes for fourteen years. Treated indifferently for that period. At time of examination she suffered from neuralgia, weakness, polyuria, polydipsia, polyphagia, and pruritis. The urine contained 6 per cent. glucose in the twenty-four-hour specimen; no protein or casts. Blood pressure: systolic, 150; diastolic, 90. Her morning blood sugar was 0.23 and 0.225 per cent. on two occasions, the

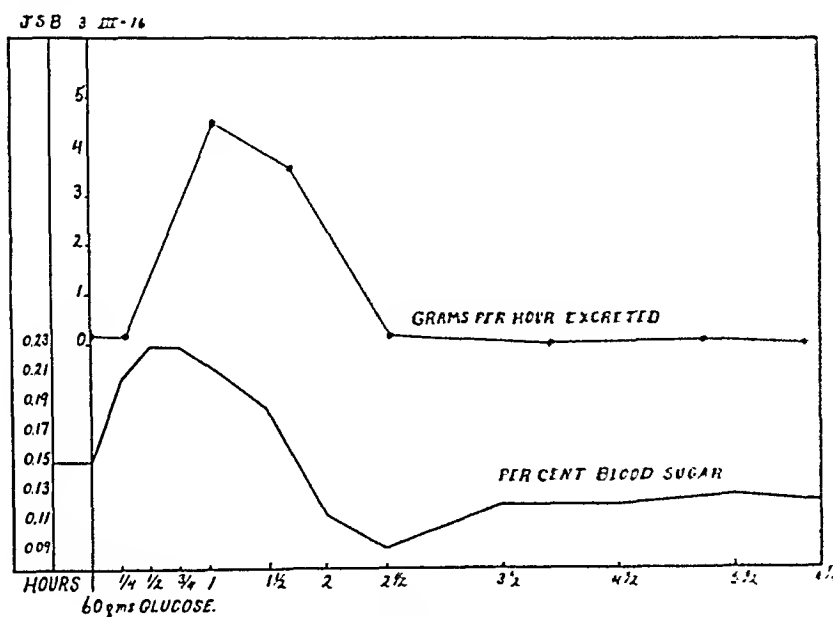


Chart 7

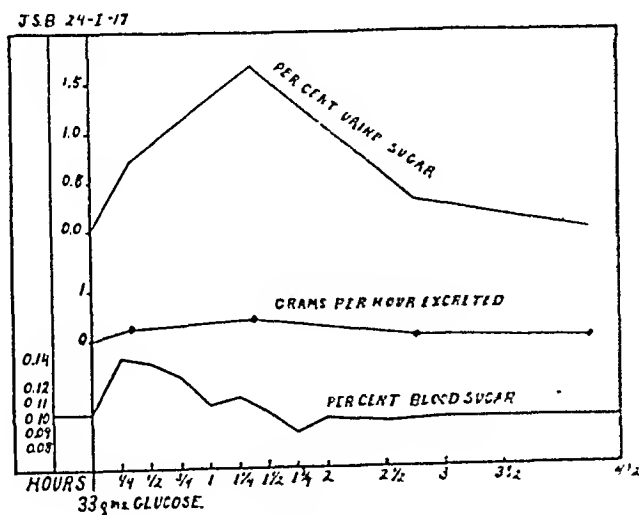


Chart 8

urine passed at the same period being free from sugar. Dec. 17, 1915, she was tested with 66 gm. of glucose. The results are shown in Chart 9 and Table 6. In this case the preformed sugar was high (0.22 per cent.), the blood sugar increased rapidly, reaching its highest point in three-quarters of an hour, and then quickly decreased. Unfortunately, specimens of blood could not be obtained after the 2 3/4-hour period. The urine at the beginning of the test was free from sugar.

TABLE 6 (CASE 4, S. O., 12/15/17).—ALIMENTARY GLUCOSE TEST ON A CASE OF DIABETES WITHOUT KIDNEY INVOLVEMENT

Time		Blood		Urine				Fluid Intake, C.c.
		Hemo-globin, Units	Sugar, per Cent.	C.e. per Hour	Sp. Gr.	Sugar		
A. M.	Hr.					Per Cent.	Gm. per Hour	
9:45	...	69	0.22	33.6	1.019	0.0	0.0	600
10:00	66 gm. glucose	30.0	1.025	0.2	0.06	
10:15	1/4	69	0.384	147.6	1.026	3.1	4.57	
10:30	1/2	68	0.432					
10:45	3/4	68	0.492	210.0	1.025	4.9	10.29	
11:00	1	68	0.49					
11:15	1 1/4	68	0.472	150.0	1.030	6.5	9.75	
11:30	1 1/2	68	0.448					
11:45	1 3/4	68		129.6	1.032	6.2	8.03	250
12:00 M.								
P. M.				60.0	1.031	5.3	3.18	
12:15	2 1/4	69	0.36					
12:30				60.0	1.031	5.3	3.18	
12:45	2 3/4	69	0.32					
1:00	48.0	1.015	0.1	0.04	
1:30	154.2	1.005	0.0	0.0	
2:10					

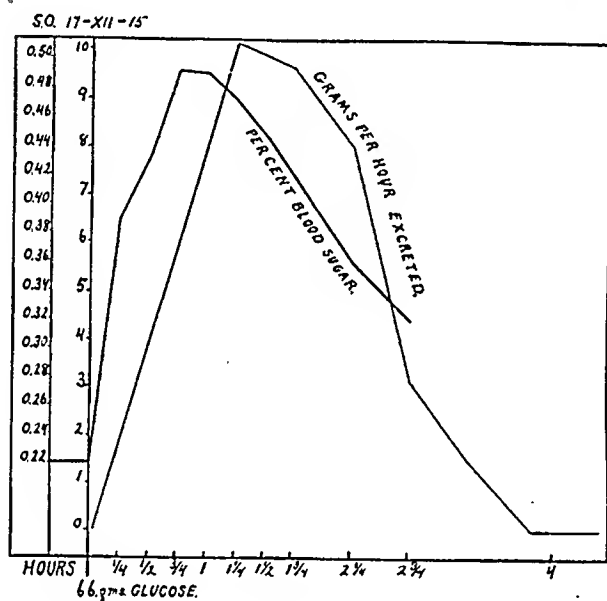


Chart 9

One cannot determine at what blood sugar concentration the kidneys actively excreted glucose, but it was between 0.22 and 0.384 per cent. The excretion of sugar was marked; it followed the blood sugar curve, and could no longer be detected with Benedict's solution at the end of four hours' time. Urine excretion decreased in the first quarter of an hour, later being uninfluenced by the increasing blood sugar. The blood volume (indicated by hemoglobin) was but slightly affected, increasing 1 per cent. This is due to the rapid response of the kidneys to fluid intake.

ALIMENTARY HYPERGLYCEMIA IN DIABETES

Alimentary hyperglycemia in diabetes, following the ingestion of glucose, has been frequently studied. Hopkins¹¹ examined nine cases and found a high preformed blood sugar value. Following the administration of 100 gm. of glucose there was a markedly prolonged hyperglycemia. Similar results have been found by Epstein,¹² Hamman and Hirschman,¹³ and Cummings and Piness.¹² Chart 10 is a composite from tests made by Epstein on cases of diabetes without renal involvement; Chart 11 from tests made by the same author in cases

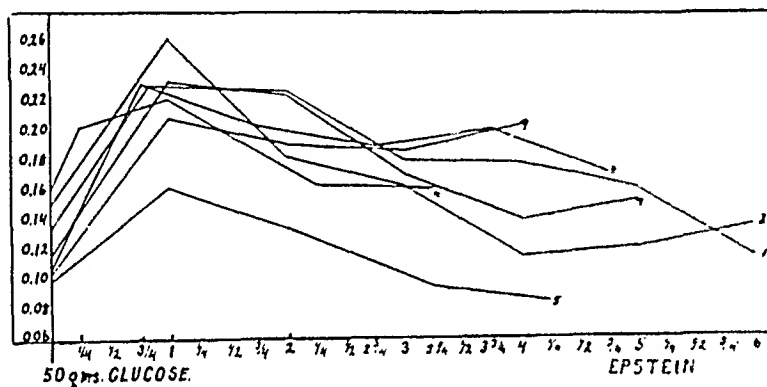


Chart 10

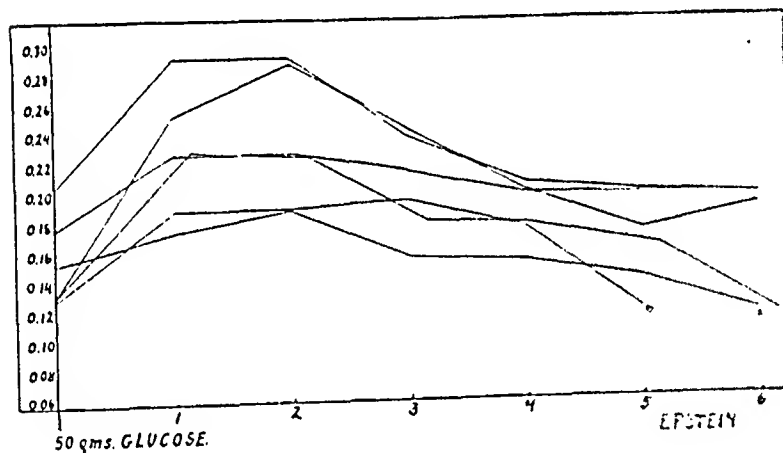


Chart 11

of diabetes with renal involvement. The effect of the nephritis was to increase the preformed blood sugar value and to prolong the hyperglycemia.

Alimentary Glucose Test in a Case of Chronic Interstitial Nephritis

CASE 5.—V. A., male, aged 27, had hemorrhagic nephritis following erysipelas seven years previous to admission. Frequent repeated attacks of great severity. At present, cardiac and vascular hypertrophy, retinitis; blood pressure: systolic, 235; diastolic, 160. Urine, 1,500 c.c.; specific gravity, 1.010; protein, moderate amount; an occasional granular cast; no sugar. Phenol-

sulphonaphthalein excretion, 8 per cent. in two hours. Blood chemistry: sugar, 0.165 per cent.; uric acid, 10.5 mg. per 100 c.c.; creatinin, 8.3 mg. per 100 c.c.; urea nitrogen, 59 mg. per 100 c.c.; combines 50 c.c. carbon dioxide per 100 c.c. of plasma.

TABLE 7 (CASE 5, V. A., 11/18/16).—ALIMENTARY GLUCOSE TEST IN A CASE OF CHRONIC INTERSTITIAL NEPHRITIS

Time		Blood			Urine				Fluid Intake, C.c.
		Hemo- globin, Units	Sugar		C.c. per Hour	Sp. Gr.	Sugar		
			In Whole Blood, per Cent.	In Plasma, per Cent.			Per Cent.	Gm. per Hour	
A. M.	Hr.								
9:00	...	59	0.159	0.147	58.0	1.010	0.0	0.0	330
9:15	75 gm. glucose	45.0	1.014	0.0	0.0	
9:30	¼	57	0.188	0.172					
9:40									
9:45	½	56	0.252	0.234					
10:00	¾	57	0.287	0.266					
					30.0	1.012	+	240
10:20	1+	58	0.296	0.272					
10:30									
10:45	1½	58	0.369	0.351					
					54.0	1.022	0.5	0.27	220
11:15	2	59	0.342	0.36					
11:30									
11:45	2½	58	0.296	0.296	220
					66.0	1.006	0.1	0.06	
P. M.									
12:20	3	59	0.228	0.222					
12:30									
1:15	4	59	0.156	0.15	54.6	1.014	+		450
1:30	
2:00	56.4	1.014	0.0	0.0	
2:15	5	59	0.126	0.117	60.0	1.010	0.0	0.0	
3:10									
3:15	6	59	0.144	0.132	60.0	1.014	0.0	0.0	220
3.45									

Feb. 18, 1916, he was tested with 75 gm. of glucose. The results are shown in Chart 12, Table 7. The preformed sugar is high, as is found in nephritis. The kidneys become permeable to sugar between 0.25 and 0.3 per cent. blood sugar. The blood sugar curve is delayed and prolonged, the highest point being reached in one and one-half hours, and the patient's normal not being regained before the four-hour period. The excretion of sugar is very slight, 0.27 gm. per hour being excreted with a blood sugar of 0.369 per cent.

Hemoglobin estimations show a 3 per cent. increase, which slowly returns to normal with the blood sugar. The excretion of urine decreases during the development of the hyperglycemia.

ALIMENTARY HYPERGLYCEMIA IN NEPHRITIS

Alimentary hyperglycemia in nephritis has been studied by Neubauer,²⁴ Tachau,²⁵ Hopkins,¹¹ Epstein,²¹ Hamman and Hirschman¹³ and others, following the administration of glucose by mouth (usually 100 gm.). Chart 13 is a composite of the results of the test in four patients examined by Hopkins; Chart 14 is a composite of the six cases of Hamman and Hirschman. In all of these cases

24. Neubauer: Biochem. Ztschr. 25:284, 1910.

25. Tachau: Deutsch. Arch. f. klin. Med. 104:448, 1911.

the curve is similar to that found in many cases of diabetes and shows the fallacy of alimentary hyperglycemic tests alone as a diagnostic method. Especially is this true of the practice of testing the blood at one-hour intervals, for in nephritis, as well as in diabetes (with renal involvement), the second hour specimen is apt to contain as much or more glucose than the first hour specimen.

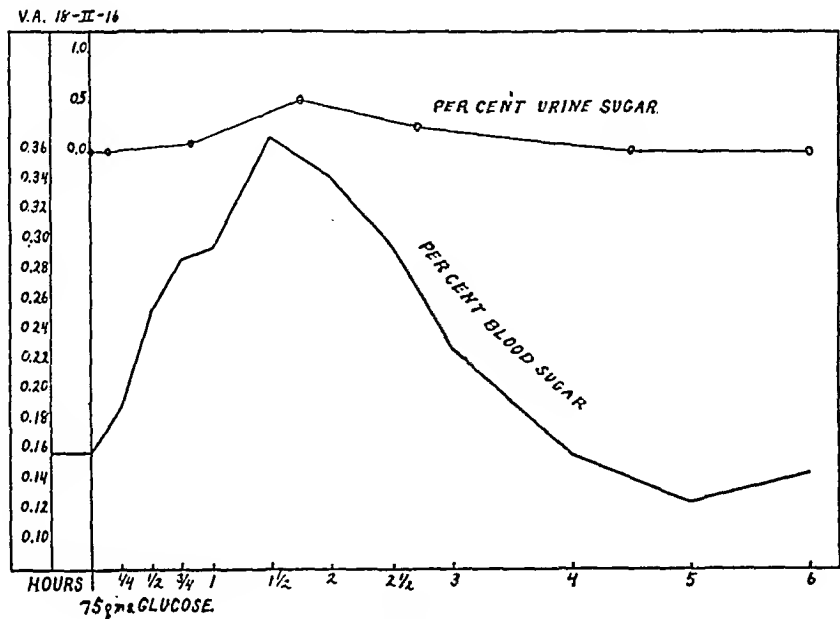


Chart 12

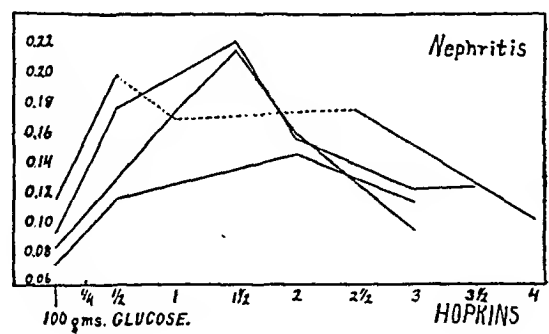


Chart 13

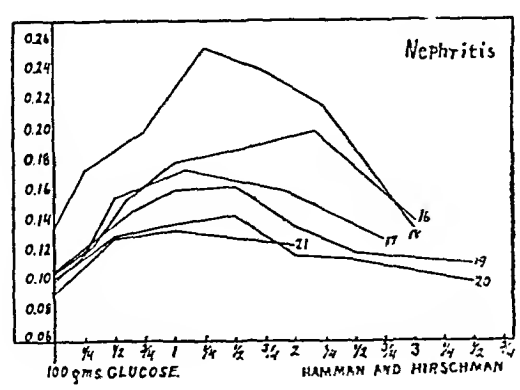


Chart 14

Alimentary Glucose Test in Diabetes with Renal Involvement

CASE 6.—C. M., male, aged 54. Glycosuria was discovered a few years prior to admission. The patient suffered from cardiac decompensation, dilatation, irregular pulse, edema, ascites, and dyspnea. The urine contained a moderate amount of protein and many hyaline and granular casts. Phenol-sulphonephthalein excreted in two hours, 29 per cent. Blood pressure: systolic, 200; diastolic, 150. Blood chemistry: sugar, 0.21 per cent.; urea nitrogen, 16 mg. per 100 c.c. blood; uric acid, 3.6 mg. per 100 c.c. blood; creatinin, 2.9 mg. per 100 c.c. blood.

TABLE 8 (CASE 6, C. M., 12/9/15).—ALIMENTARY GLUCOSE TEST IN DIABETES WITH RENAL INVOLVEMENT

Time		Blood		Urine				Fluid Intake, C.c.
		Hemo-globin, Units	Sugar, per Cent.	O.e. per Hour	Sp. Gr.	Sugar		
						Per Cent.	Gm. per Hour	
A. M.	Hr.							
9:15	...	81.5	0.21	72	1.011	0.0	0.0	250
9:30	33 gm. glucose	?	0.0	0.0	
9:45	1/4	81.5	0.24		?			
10:00	1/2	77.0	0.288					250
10:15	3/4	78.0	0.308	48	1.015	++	?	
10:30	1	80.0	0.301					
10:45	1 1/4	80.0	0.301	96	1.013	0.61	0.58	250
10:50								250
11:15	1 3/4	81.0	0.252	114	1.010	0.153	0.17	250
11:45	2 1/4	81.0	0.25	90	1.011	++	?	
P. M.								
12:15	2 3/4	81.5	0.235	120	1.011	+	?	
12:45	3 1/4	81.5	0.23	204	1.008	0.0	0.0	
1:15	3 3/4	83.0	0.215	120	1.012	0.0	0.0	
1:45	4 1/4	82.0	0.210	102	1.010	0.0	0.0	
2:45	5 1/4	81.5	0.205	72	1.010	0.0	0.0	

Dec. 9, 1915, he was tested with 33 gm. of glucose. The results are shown in Chart 15 and Table 8. The striking features are the high preformed blood sugar value, the rapid rise in blood sugar, reaching its highest point in three-quarters of an hour, the great delay in returning to normal (four and one-fourth hours), and the very slight excretion of sugar.

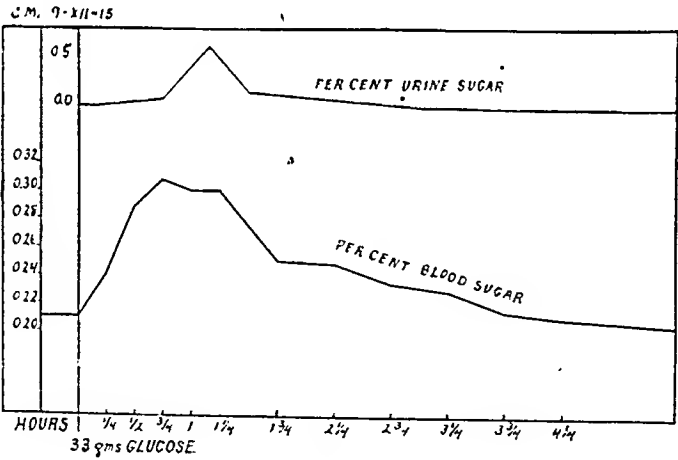


Chart 15

Blood volume increased 4.5 per cent. (as indicated by hemoglobin) during the hyperglycemia, later returning to normal. Urinary excretion fell off markedly, greatly increasing as the hyperglycemia subsided.

CASE 7.—I. A., female, aged 46. Diabetes eleven years. Chronic interstitial nephritis. Daily urine contained from 3 to 6 per cent. sugar on ordinary diet, a trace of albumin, and a few hyaline and granular casts. Blood chemistry: sugar, 0.26 per cent.; urea nitrogen, 30 mg. per 100 c.c. blood; uric acid, 6 mg. per 100 c.c. blood; creatinin, 3 mg. per 100 c.c. blood. Phenol-sulphonaphthalein, 52 per cent. excreted in two hours. Morning urine free from sugar.

TABLE 9 (CASE 7, I. A., 11/1/16).—DIABETES WITH RENAL INVOLVEMENT

Time		Blood		Urine						Fluid Intake, C.c.
		Hemo- globin, Units	Sugar, per Cent.	O.e. per Hour	Sugar		Chlorids, Gm. per Hour	Sp. Gr.		
					Bene- dict's Method, per Cent.	Myers Method Per Cent.			Gm. per Hour	
A. M.	Hr.									
9:15	...	67	0.255	36.0	0.125	0.12	0.043	0.201	1.018	400
9:30	30 gm.	glucose	
				233.0	0.15	0.159	0.37	1.302	1.012	
9:45	1/4	64	0.275							
10:00	1/2	64	0.352	258.0	0.72	0.54	1.39	0.516	1.010	
10:15	3/4	61	0.424							
				468.0	1.4	1.08	5.05	0.748	1.008	
10:30	1	63	0.441							
10:45	1 1/4	64	0.459	420.0	1.58	1.41	5.92	0.714	1.010	
11:00	1 1/2	64	0.459							
11:15	1 3/4	65	0.45	170.0	2.88	2.12	3.6	0.577	1.015	
11:30	2	66	0.441							
11:45	2 1/4	66	0.413							
12:00 M.	2 1/2	67	0.392	117.0	2.76	2.35	2.75	0.444	1.019	
P. M.										
12:10										
12:30	3	66	0.364	94.0	2.58	2.0	1.87	0.374	1.020	
12:45										
1:00	3 1/2	68	0.343	52.0	2.22	2.0	1.03	0.258	1.023	
1:15										
1:30	4	68	0.31	40.0	2.13	2.04	0.8	0.213	1.021	
2:00	4 1/2	68	0.30							
2:30	5	68	0.29	38.0	1.68	1.47	0.55	0.226	1.025	
3:00	5 1/2	69	0.275							
3:30	6	70	0.26	39.0	0.92	0.77	0.3	0.27	1.026	
4:00	6 1/2	70	0.255							
4:30	7	70	0.24	39.0	0.92	0.78	0.3	0.226	1.025	
5:00	7 1/2									

Nov. 1, 1916, she was tested with 30 gm. of glucose. The results are shown in Chart 16 and Table 9. The interesting points are the high preformed sugar value, the rapid and high hyperglycemia, the delay in returning to normal, and the permeability point to glucose being but slightly above the preformed sugar value, explaining the rapid appearance of glycosuria.

Alimentary Glucose Test in a Case of Hyperthyroidism

CASE 8.—J. K., male, aged 42, for the previous four months had weakness, loss of weight, irritability, tremors, palpitation, tachycardia, exophthalmos, enlarged pulsating thyroid, and glycosuria following meals. On the morning of May 20, 1915, he was given a hypodermic injection of 0.66 mg. of epinephrin. The results are shown in Chart 17 and Table 10. The preformed sugar was at the highest normal limit, probably due to his anxiety over the test. The kidneys actively excreted sugar when the blood sugar was between 0.165 and 0.171 per cent. Blood volume increased 3 per cent. during the development of the hyperglycemia (as shown by hemoglobin).

May 26, 1915, he was again tested with 1 mg. epinephrin hypodermically. The results are shown in Chart 18 and Table 11. Sugar appeared in the urine at a blood sugar concentration of 0.165 per cent. The hyperglycemia was more rapid, higher and more prolonged than when the smaller amount of epinephrin was given.

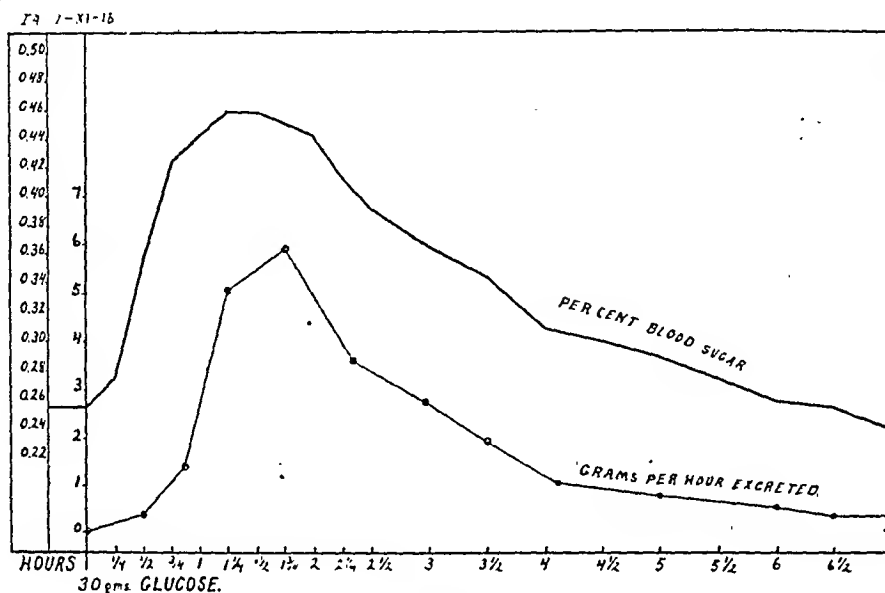


Chart 16

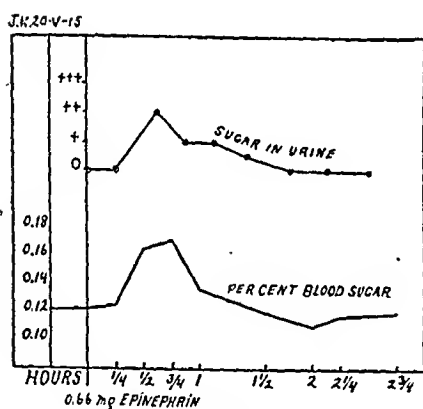


Chart 17

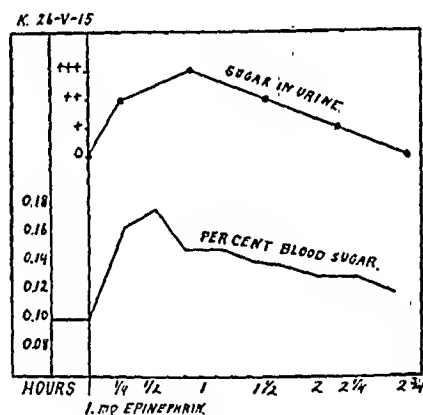


Chart 18

May 28, he was tested with 33 gm. of glucose. The results are shown in Chart 19 and Table 12. The blood sugar curve is of the normal type. Sugar was excreted at a blood sugar concentration between 0.15 and 0.174 per cent. Blood volume increased 5 per cent.

In these three tests the excretion of sugar closely followed the changes in blood sugar.

Alimentary Glucose Test in a Case of Myxedema

CASE 9.—M., male, aged 54, for the previous four years had obesity, falling hair, lassitude, mental hebetude, myxedema of face, limbs, and abdomen, atrophy of thyroid gland and myocarditis. Blood pressure: systolic, 125; diastolic, 85. Phenolsulphonephthalein excreted in two hours time, 53 per

TABLE 10 (CASE 8, J. K., 5/20/15).—ALIMENTARY GLUCOSE TEST IN A CASE OF HYPERTHYROIDISM

Time		Blood Pressure	Blood		Urine Sugar	Fluid Intake, C.e.
A. M.	Hr.		Hemoglobin Units	Sugar, per Cent.		
10:25	...	132-50	72	0.122	0.0	250
10:30	0.66 mg. epinephrin (hypo.)	160-70	69	0.124	0.0	
10:45	1/4	140-75	69	0.165	0.0	
11:00	1/2	138-72	69	0.171	++	
11:15	3/4	133-60	69	0.136	+	
11:30	1	250
11:45	
P. M.						
12:05	1 1/2	125-63	69	0.12	0	
12:30	2	130-64	70	0.11	0.0	
12:45	2 1/4	132-65	70	0.118	0.0	
1:15	2 3/4	140-68	72	0.12	0.0	

TABLE 11 (CASE 8, J. K., 5/26/15).—SECOND TEST WITH EPINEPHRIN

Time		Blood Pressure	Blood Sugar, per Cent.	Urine		Fluid Intake, C.e.
P. M.	Hr.			C.e. per Hour	Sugar	
1:55	...	155-75	0.1	78.0	0.0	250
2:05	1 mg. epinephrin (hypo.)	193-70	0.165	18.0	++	
2:25	1/4+	145-65	0.177	36.0	+++	
2:40	1/2+	132-60	0.147			
2:55	1 -					
3:05						
3:15	1 1/4-	130-55	0.147			
3:30	1 1/2-	125-55	0.141	49.0	++	
3:45	1 3/4-	126-60	0.134			
4:05	2	130-65	0.132			
				120.0	+	
4:25	2 1/4+	130-78	0.130			
4:45	2 3/4-	123-62	0.118	56.0	0.0	
5:00						

TABLE 12 (CASE 8, J. K., 5/28/15).—GLUCOSE TEST

Time		Blood		Urine			Fluid Intake, C.e.
A. M.	Hr.	Hemoglobin, Units	Sugar, per Cent.	C.e. per Hour	Per Cent.	Gm. per Hour	
10:05	...	75.5	0.116	?	0.0	0.0	300
10:30	33 gm. glucose	48	0.0	0.0	
10:45	1/4	71.0	0.15	78	0.27	0.05	
11:00	1/2	70.5	0.174	62	1.0	0.6	
11:15	3/4	68.0	0.188				
11:25				60	0.9	0.54	
11:30	1	69.5	0.192	63	0.5	0.3	
11:45							
12:00 M.	1 1/2	70.5	0.18				
P. M.							
12:15	48	0.2	0.09	300
12:30	2	70.5	0.129	78	0.0	0.0	
12:45							
1:00	2 1/2	71.5	0.104	62	0.0	0.0	
1:15							
1:30	3	72.0	0.118	37	0.0	0.0	
1:40							
2:00	3 1/2	76.0	0.114	42	0.0	0.0	
2:15				36	0.0	0.0	
3:15	4 3/4	74.5	0.116				
3:45	5 1/4	75.0	0.112				

cent. Blood chemistry: urea nitrogen, 20 mg. per 100 c.c. blood; uric acid, 4.2 mg. per 100 c.c. blood; creatinin, 1.7 mg. per 100 c.c. blood.

July 9, 1915, he was tested with 1 mg. of epinephrin hypodermically. The results are shown in Chart 20 and Table 13. The preformed blood sugar was of normal value. The increase in blood sugar was very slow, the highest point being reached in from one to one and one-quarter hours, and had not returned to normal at the end of three and one-half hours. The highest blood sugar value was 0.141 per cent. and at no time was sugar excreted.

July 15, he was tested with 90 gm. of glucose. The results are shown in Chart 21 and Table 14. The preformed blood sugar was within normal limits. The blood sugar curve reached its highest point in one hour, but did not return to normal before the three and one-half to four-hour period. At no

TABLE 13 (CASE 9, M., 7/9/15).—ALIMENTARY GLUCOSE TEST IN A CASE OF MYXEDEMA

A. M.	Time Hr.	Hemoglobin Units	Blood Sugar, per Cent.	Urine Sugar
9:25	...	69	0.112	0.0
9:30	1 mg. epinephrin (hypo.)			
9:45	$\frac{1}{4}$	65	0.12	0.0
10:00	$\frac{1}{2}$	70	0.132	0.0
10:15	$\frac{3}{4}$	68	0.138	
10:30	1	67	0.141	0.0
10:45	$1\frac{1}{4}$	70	0.141	
11:00	$1\frac{1}{2}$	68	0.138	
11:15	$1\frac{3}{4}$	68	0.138	0.0
11:30	2	68	0.135	
11:45	$2\frac{1}{4}$	64	0.132	
12:00 M.	$2\frac{1}{2}$	66	0.129	
P. M.				
12:15	$2\frac{3}{4}$	63	0.126	0.0
12:30	3	65	0.128	
12:45	$3\frac{1}{4}$	66	0.126	
1:00	$3\frac{1}{2}$	66	0.126	

TABLE 14 (CASE 9, M., 7/15/15).—GLUCOSE TEST

A. M.	Time Hr.	Hemo- globin Units	Blood Sugar, per Cent.	Urine Sugar, per Cent.	Fluid Intake, C.c.
9:00	...	68.0	0.12	0.0	400
9:15	90 gm. glucose	
9:45	$\frac{1}{2}$	64.0	0.188	0.0	
10:00	$\frac{3}{4}$	66.0	0.212		
10:15	1	67.0	0.216	0.0	
10:30	$1\frac{1}{4}$	68.0	0.204		
10:45	$1\frac{1}{2}$	68.0	0.2		
11:00	$1\frac{3}{4}$	68.0	0.196	0.0	
11:15	2	67.0	0.188		
11:45	$2\frac{1}{2}$	68.0	0.18		
P. M.					
12:15	3	68.0	0.156	0.0	
12:45	$3\frac{1}{2}$	68.0	0.135		
1:15	4	67.0	0.094		
1:45	$4\frac{1}{2}$	68.0	0.096	0.0	
2:15	5	67.5	0.104		
2:55	$5\frac{3}{4}$	68.0	0.106		
3:30	$6\frac{1}{4}$	68.0	0.112	0.0	

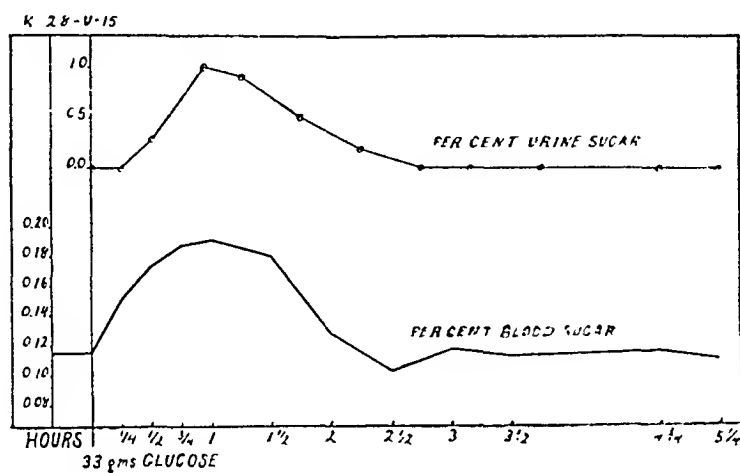


Chart 19

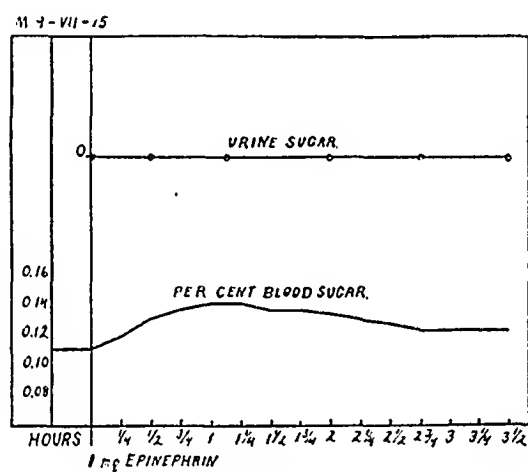


Chart 20

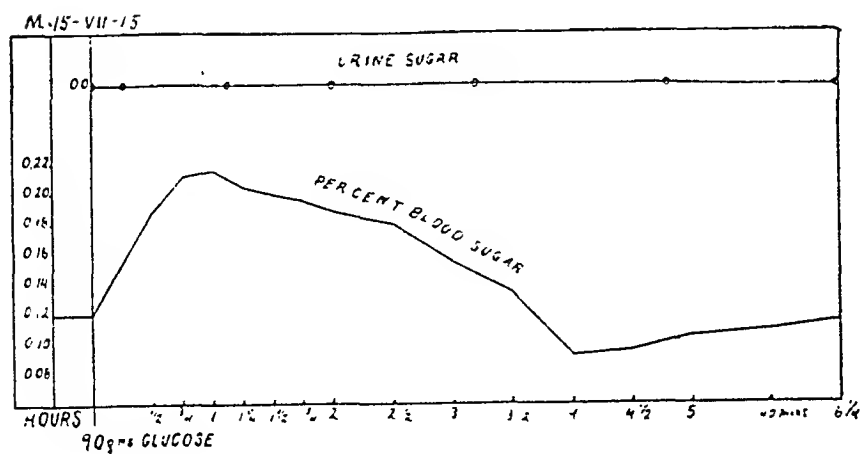


Chart 21

time was sugar excreted, although the blood sugar had reached a concentration of 0.216 per cent. Blood volume increased 4 per cent. on the development of the hyperglycemia, returning to normal as the blood sugar decreased.

The observations of Janney and Isaacson²⁶ on the blood sugar in thyroid and other endocrine diseases are of interest in connection with this and the following case.

Alimentary Glucose Test in Hypopituitarism

CASE 10.—E. L., female, aged 18, had the hypophysis removed by operation one year prior to admission. Marked obesity. Urine volume, 6,000 c.c. daily. No sugar, protein, or casts. Phenolsulphonephthalein, 62 per cent. excreted in two hours. Blood chemistry: urea nitrogen, 10 mg. per 100 c.c. blood; uric acid, 3.1 mg. per 100 c.c. blood; creatinin 1.8 mg. per 100 c.c. blood. The patient had been tested on two occasions with 250 gm. of glucose, and the twenty-four-hour specimen examined for sugar without any being found.

TABLE 15 (CASE 10, E. L., 1/31/16).—ALIMENTARY GLUCOSE TEST IN HYPOPITUITARISM

Time A. M. Hr.		Blood			Urine					Fluid Intake, C.e.
		Hemo- globin, Units	Sugar		C.e. per Hour	Sp. Gr.	Sugar		Chlorids, Gm. per Hour	
			In Whole Blood, per Cent.	In Plasma, per Cent.			Per Cent.	Gm. per Hour		
9:35	...	71	0.12	0.105	270.0	1.010	0.0	0.0	0.216	400
10:15	240 gm. glucose	
10:30	¾	71	0.259	0.224						
10:45	¾	68	0.315	0.297	36.0	1.014	0.2	0.72	0.1	
11:00	vomited 36.9 gm. glucose									
10:10										
11:15	1	67	0.369	0.351						
11:45	1½	66	0.378	0.333	288.0	1.024	0.9	2.59	0.4	
12:00 M.										
P. M.										
12:15	2	67	0.344	0.304						
1:00	2¾	67	0.287	0.252	342.0	1.023	0.4	1.36	0.27	
1:15	240
1:30	3¾	68	0.252	0.222						
2:30	4¾	68	0.184	0.16	192.0	1.009	0.0	0.0	0.102	
2:40	240
3:45	5½	68	0.105	0.066	306.0	1.022	0.0	0.0	0.24	
4:00										

Jan. 31, 1916, she was tested with 240 gm. of glucose. This was dissolved in 400 c.c. of weak tea and administered by means of a small stomach tube. The results are shown in Chart 22 and Table 15. The preformed blood sugar was within normal limits. Alimentary hyperglycemia reached its highest point in one and one-half hours, and returned to normal in five and one-half hours. Notwithstanding the high concentration of blood sugar, 0.378 per cent., the excretion of glucose was comparatively slight. Sugar was actively excreted at a blood sugar concentration of 0.26 per cent.

26. Janney and Isaacson: Arch. Int. Med. 22:160, 1918.

The excretion of urine greatly decreased in the three-quarters hour following the ingestion of the glucose, later increasing. The excretion of chlorids decreased as the glucose solution was being absorbed.

Blood volume increased 5 per cent. (as indicated by hemoglobin decrease) during the hyperglycemia, later returning to normal.

Alimentary Glucose Test in a Case of Dyspituitarism

CASE 11.—S., male, aged 27, was obese, of feminine figure, with small wrists, tapering fingers, beardless face, and was mentally inferior. His morning blood sugar was 0.1 per cent.

TABLE 16 (CASE 11, S., 5/12/16).—ALIMENTARY GLUCOSE TEST IN A CASE OF DYPITUITARISM

Time		Blood				Urine			Fluid Intake, C.c.
		Hemo- globin, Units	Sugar			C.c. per Hour	Sp. Gr.	Sugar	
			In Whole Blood, per Cent.	In Plasma, per Cent.	In Cor- puscles, per Cent.				
A. M.	Hr.								
9:25	...	75	0.132	0.10	0.123	30	1.025	0	400
9:30	75 gm. glucose		25	1.030	0	
9:45	1/4	72	0.178	0.2	0.2				
10:00	1/2	70	0.198	0.197	0.188				
10:15	3/4	69	0.193	0.18	0.172	21	1.033	0	
10:40	1 1/4	70	0.183	0.156	0.172				
11:00	1 1/2	69	0.148	0.14	0.155	43	1.036	0	
11:30	2	71	0.132	0.111	0.134				
12:00 M.	2 1/2	73	0.118	0.094	0.128	20	1.041	0	
P. M.									
12:30	3	74	0.097	0.086	0.114	21	1.040	0	
1:15	3 3/4	74	0.111	0.099	0.123	21	1.043	0	
2:00	4 1/2	73	0.111	0.114	0.128				
2:30	5	74	0.112	0.105	0.141	16	1.043	0	
3:00	5 1/2	76	0.118	0.111	0.141	15	1.040	0	
4:00	6 1/2	75	0.108	0.111	0.141				

May 12, 1916, he was tested with 75 gm. of glucose. The results are shown in Chart 23 and Table 16. The preformed blood sugar was slightly above normal. The blood sugar curve was of normal type. The urine remained free from sugar, although the blood sugar had reached a concentration of 0.198 per cent. The excretion of urine decreased during the development of the hyperglycemia, increasing as the blood sugar began to fall.

Hemoglobin estimations showed a blood volume increase of 6 per cent., which returned to normal with the blood sugar.

Alimentary Glucose Test in a Case of Parenchymatous Nephritis with Constant Glycosuria

CASE 12.—J. P., male, aged 62, had symptoms of nephritis for the previous two years. No symptoms of diabetes mellitus. For the previous six months he had generalized edema, retinitis, cardiac hypertrophy. Blood pressure: systolic, 190; diastolic, 130. Urine, 625 c.c., specific gravity, 1.025; dry protein per liter, 3.1 gm.; chlorids, 6.6 gm.; sugar, 0.6 per cent.; many hyaline and granular casts. Phenolsulphonephthalein excreted in two-hour test, 8 per cent. Blood chemistry: sugar, 0.18 per cent.; urea nitrogen, 23 mg.; uric acid, 4 mg.; creatinin, 1.9 mg. per 100 c.c. of blood. For ten months, up to the time of the patient's death, the urine constantly contained glucose, the concentration always being in the neighborhood of 0.5 per cent.

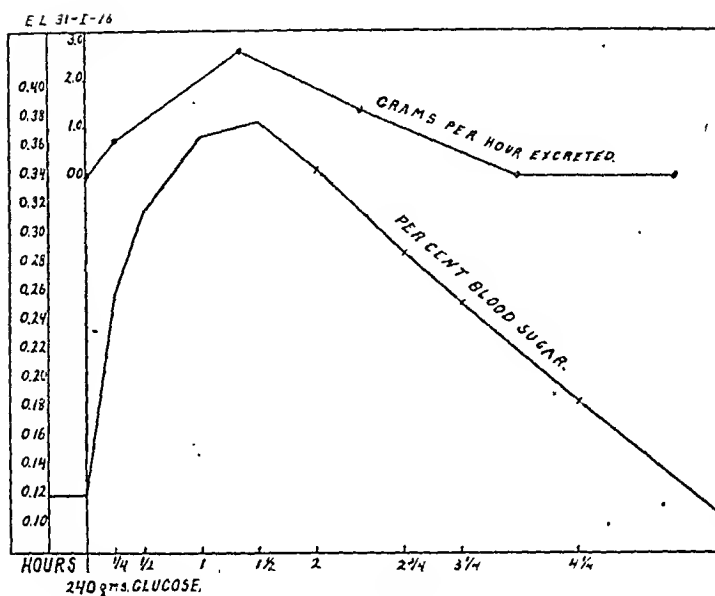


Chart 22

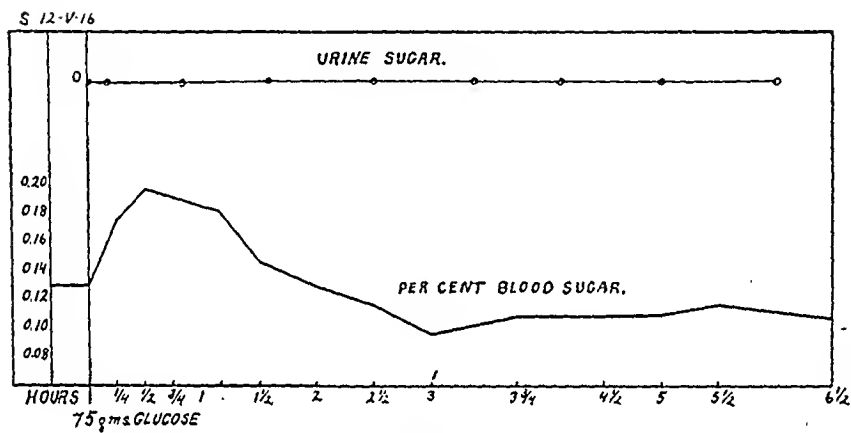


Chart 23

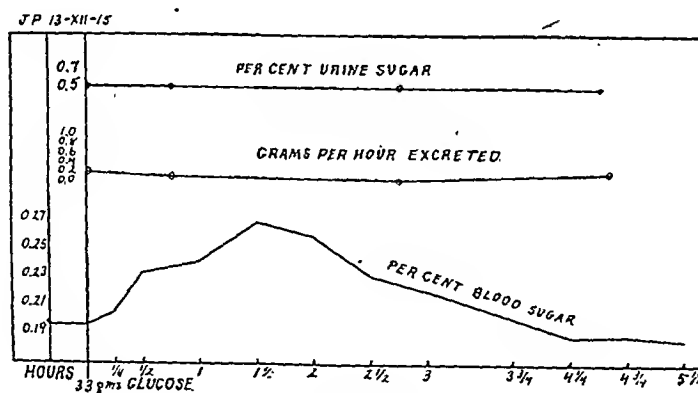


Chart 24

Dec. 13, 1915, the patient was tested with 33 gm. of glucose. The results are shown in Chart 24 and Table 17. The preformed blood sugar was high, as commonly found in nephritis. The blood sugar curve was greatly prolonged, the highest point being reached in one and one-half hours, not returning to normal before four and one-half hours had elapsed. The urine passed in this period contained about 0.5 per cent. glucose, and this independent of the blood sugar concentration. The actual excretion of glucose was less during the hyperglycemia than during the fasting state. In this case the sugar excretion varied directly with the excretion of urine.

March 11, 1916, the test was repeated, using 75 gm. of glucose. The results are shown in Chart 25 and Table 18. Again in this test the excretion of glucose was less during the hyperglycemia, although the urine sugar increased to 1.1 per cent. The time periods for the blood sugar curve are slightly longer than in the previous test; less than half the amount of glucose was ingested.

In each of these tests the excretion of urine decreased following the ingestion of glucose. Hemoglobin decreased during the development of the hyperglycemia, indicating an increase in blood volume at this time. The volume returned to normal on the subsidence of the hyperglycemia. Table 17 shows a decreased excretion of chlorids as the blood sugar increased. This retention is probably due to the increase in body fluid from the fluid intake and decreased excretion of urine.

TABLE 17 (CASE 12, J. P., 12/13/15).—GLUCOSE TEST IN PARENCHYMATOUS NEPHRITIS WITH CONSTANT GLYCOSURIA

Time		Blood		Urine					Fluid Intake, C.e.
		Hemo- globin, Units	Sugar, per Cent.	C.e. per Hour	Sugar		Sp. Gr.	Chlorids, Gm. per Hour	
					Per Cent.	Gm. per Hour			
A. M.	Hr.								
9:25	...	67.5	0.196	42	0.52	0.22	1.015	0.193	250
9:30	33 gm. glucose	
9:45	$\frac{1}{4}$	64.0	0.208	36	0.51	0.186	1.015	0.123	
10:00	$\frac{1}{2}$	65.0	0.234						
10:30	1	65.5	0.24						
11:00	$1\frac{1}{2}$	67.5	0.27	33	0.51	0.17	1.016	0.142	
11:30	2	67.0	0.26						
12:00 M.	$2\frac{1}{2}$	68.0	0.232						
P. M.									
12:30	3	67.5	0.224	42	0.52	0.21	1.013	0.19	
1:15	$3\frac{3}{4}$	67.5	0.204						
1:30									
1:45	$4\frac{1}{4}$	67.5	0.196	42	0.52	0.21	1.013	0.19	
2:15	$4\frac{3}{4}$	68.0	0.196						
2:45	$5\frac{1}{4}$	67.5	0.192						

SUMMARY

In the series of cases reported one finds variations in the blood sugar value after fifteen hours' fasting. Normal values are found in cases of renal diabetes, early mild diabetes, hyperthyroidism, hypothyroidism, hypopituitarism, dyspituitarism, and in a normal case. High blood sugar values are found in cases of nephritis, and diabetes of long standing with or without renal involvement. In the synchronous urine specimens two only showed the presence of glucose by Benedict's test. One was from a patient with a blood sugar of 0.098 per cent. whose kidneys at that time were excreting glucose at the rate of 2 gm. per hour. The other case showed a constant glycosuria of 0.5 per cent. independent of the diet.

In the twenty-four-hour urine specimens, glucose was found in the cases of renal diabetes, early mild diabetes, diabetes with and without renal involvement, hyperthyroidism, and chronic parenchymatous nephritis with constant glycosuria.

TABLE 18 (CASE 12, J. P., 3/11/16).—SECOND TEST

Time		Blood		Urine				Fluid Intake, C.c.
		Hemo- globin, Units	Sugar, per Cent.	C.c. per Hour	Sp. Gr.	Sugar		
						Per Cent.	Gm. per Hour	
A. M.	Hr.							
9:20	...	65.0	0.2	144	1.015	0.5	0.72	450
9:30	75 gm. glucose	
9:45	1/4	65.0	0.258					
10:05	1/2	65.0	0.256					
10:20	3/4	64.0	0.252	52	1.013	1.0	0.52	250
10:35	1	64.0	0.329					
11:00	1 1/2	63.5	0.368					
11:20								
11:30	2	63.5	0.405					500
P. M.								
12:45	3 1/4	64.0	0.39	56	1.015	1.1	0.61	
1:30								
3:15	5 3/4	65.0	0.25					
4:15	6 3/4	65.0	0.22	?	1.014	0.5	?	
7:35								

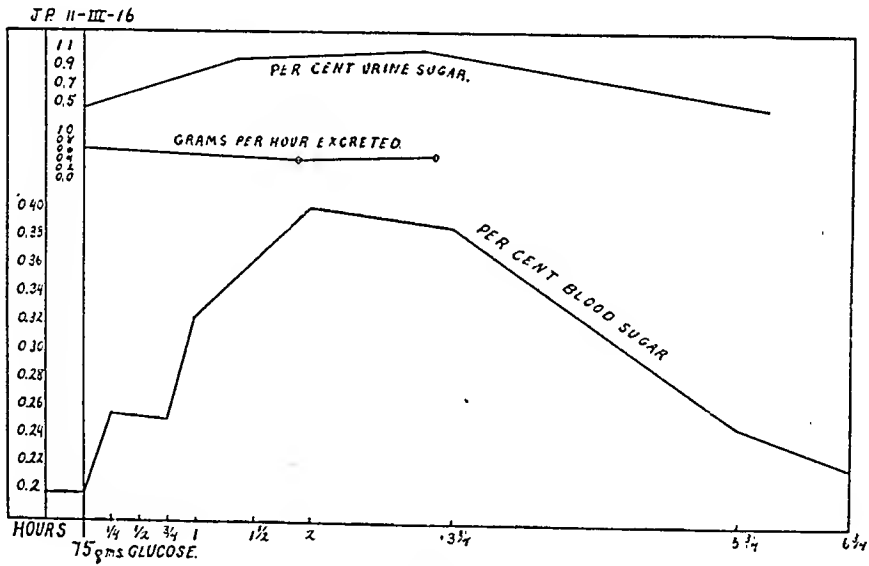


Chart 25

Following the ingestion of glucose the type of blood sugar curve varied in the different cases, showing a rapid increase and decrease in uncomplicated mild diabetes; in the cases of dyspituitarism, hyperthyroidism, renal diabetes, and normal, the curves are of the type found in normal individuals by various investigators.

In nephritis the curve was delayed and prolonged. In diabetes with renal involvement, the increase in blood sugar was at the normal rate, but there was a very slow return to the preformed value.

A higher blood sugar at the end of the first hour than at the end of the second was found in normal, renal diabetes, early mild diabetes, diabetes of long standing without renal involvement, diabetes with cardiac incompetence, hyperthyroidism, myxedema, hypopituitarism, and dyspituitarism.

Higher values at the end of the second hour were found in chronic interstitial nephritis, diabetes with interstitial nephritis, and chronic parenchymatous nephritis with constant glycosuria.

The concentration of blood sugar at which glycosuria occurred varied greatly in these cases, being less than 0.088 per cent. in the case of renal diabetes, 0.125 per cent. in early mild diabetes, 0.165 per cent. in hyperthyroidism, 0.167 per cent. in the normal case, 0.2+ per cent. in dyspituitarism, 0.216 per cent. in hypothyroidism, 0.26+ per cent. in hypopituitarism, 0.29 per cent. in nephritis, and 0.3+ per cent. in two cases of diabetes with renal involvement.

Cases showing an excretion of over 1 gm. of sugar in the six hours following the ingestion of from 60 to 75 gm. of glucose were: renal diabetes, early mild diabetes, diabetes of long standing without renal involvement, parenchymatous nephritis with constant glycosuria, those excreting less than 1 gm. were normal, interstitial nephritis, myxedema and dyspituitarism.

Cases showing an excretion of more than 1 gm. in the six hours following the ingestion of 30 to 33 gm. of glucose were renal diabetes, diabetes with renal involvement, parenchymatous nephritis with constant glycosuria; those excreting less than 1 gm. were: early mild diabetes, diabetes with cardiac incompetence, and hyperthyroidism.

The rate of sugar excretion was uninfluenced by changes in excretion of urine in all excepting Case 12. In this patient glycosuria varied directly with the amount of urine excreted and not according to changes in the blood sugar. A similar case has been reported by Epstein²¹ (Chart 26).

Sixty estimations are given comparing the sugar content of whole blood and that of plasma. The results show 15 per cent. more in whole blood than in plasma. (A source of error in the technic employed lies in the fact that the plasma specimens were allowed to stand at room temperature for half an hour, during which time glycolysis may have occurred; the whole blood estimates were made at once.)

In twenty-six estimations the corpuscles contained 5 per cent. more reducing substance than the plasma (the technic being the same for both).

In thirteen tests, changes in blood volume were recorded following the ingestion of glucose. During the rise in blood sugar, blood volume increased from 1 to 7.5 per cent. (the average increase being 4.2 per cent.). The volume returned to normal on the subsidence of the hyperglycemia.

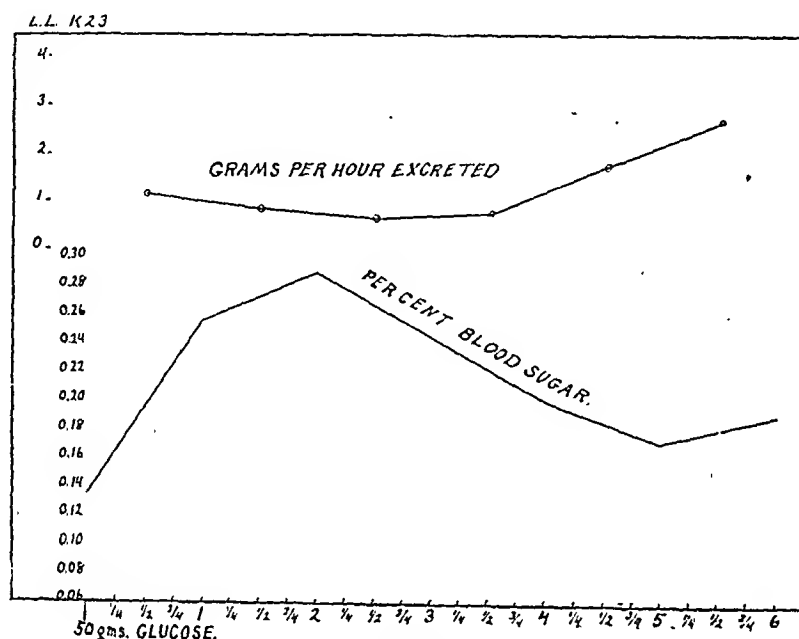


Chart 26

CONCLUSIONS

1. Sugar is a constant constituent of normal urine, and, during a fasting and thirsting state, the concentration in the urine approximates that in the blood.
2. Following the administration of small amounts of glucose (30 gm. or less) the blood sugar increases, and its demonstration depends entirely on the frequency of the estimations.
3. In a normal person the sugar in the urine parallels that in the blood up to the latter's concentration of 0.16 to 0.17 per cent. Above that the kidneys actively excrete sugar. In returning to the normal value the decrease in blood sugar precedes that in the urine.
4. Alimentary hyperglycemia in uncomplicated diabetes is characterized by a rapid rise and fall.
5. When diabetes is complicated by renal involvement, alimentary hyperglycemia is prolonged.
6. Alimentary hyperglycemia is prolonged in myxedema and hypopituitarism.
7. In nephritis alimentary hyperglycemia is delayed and prolonged.

8. The concentration of blood sugar at which glycuressis occurs varies in different individuals, and is influenced by disease, being abnormally low in early diabetes, high in diabetes of long standing, in nephritis, and in deficiency of the thyroid or hypophysis.

9. Glycuressis is a kidney function and is excessive in diabetes and hyperthyroidism. It is greatly decreased in nephritis and in deficiency of the thyroid or hypophysis.

10. Blood sugar estimations one hour after the ingestion of glucose may be the same in renal diabetes, early diabetes, or normal cases.

11. Blood sugar estimations two hours and three hours after the ingestion of glucose may be the same in diabetes of long standing, in nephritis, myxedema, or in hypopituitarism.

12. Blood volume increases with the development of a hyperglycemia, returning to normal with the blood sugar.

13. Blood sugar is about equally divided between plasma and corpuscles.

14. Sugar in the corpuscles increases in proportion to that in the plasma.

15. Excretion of sugar is uninfluenced by the rate of urinary excretion, excepting in some cases of parenchymatous nephritis.

16. Morning blood sugar estimations are of great diagnostic value. The urine excreted at the same time should be tested for sugar and the rate of excretion determined. As the morning blood sugar varies under treatment, diagnostic tests should be made after the patient has been on regular diet for several days.

17. Tests of alimentary hyperglycemia are of little clinical value; especially is this true of tests made at one hour intervals.

18. Examination of the twenty-four-hour urine for sugar (Benedict's new method²⁷), or better, fractional examinations, detects cases of excessive glycuressis.

19. Test of alimentary glycuressis following the ingestion of glucose (100 gm. for a person of average weight, that is, 1.7 gm. per kilogram) is a valuable diagnostic and prognostic method, the urine sugar being estimated at frequent intervals for the succeeding six hours, and the total excretion determined. This, in conjunction with the morning blood and synchronous urine sugar estimation, probably tells us as much about the case as do the elaborate tests herein reported.

I wish to thank Prof. Edward Quintard, director of the Department of Medicine, and Prof. Victor C. Myers, director of the Laboratory of Pathological Chemistry, for their many courtesies, help and advice.

303 East Twentieth Street.

27. The conclusions regarding clinical tests are largely in accord with those of Rogers: *Boston M. & S. J.* 175:152 (Aug. 3) 1916.

DIASTATIC ACTIVITY OF THE BLOOD IN CANCER, SYPHILIS AND DIABETES*

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Some interesting observations were made by V. C. Meyers and J. A. Killian¹ on the diastatic activity of the blood, and we have for some months past included an estimation of the diastatic activities of the blood in our routine complete blood studies. We have followed the method of Lewis and Benedict for blood sugar estimation and that of Meyers and Killian for the diastatic activity in the blood, being exact in the period of incubation, and beginning the blood chemistry work within ten minutes after the withdrawal of blood from the vein.

In the routine studies of the blood of cancer patients of the State Institute for the Study of Malignant Disease we have accumulated considerable data on other estimable blood factors, but in this short paper we are reporting only on the Wassermann reaction, diastatic activity and sugar content of the blood, and the effect of roentgen-ray treatments on these factors. We have also included in our report similar studies of diabetics and nephritics, eclamptics, cases of general fatigue and overwork, and normal people. The most interesting of our observations have been those made in our studies of the cases of diabetes, in the behavior of the diastatic activity of the blood. After an observation of a large series of cases we have taken this factor to be normal up to an activity of 40.

DIASTATIC ACTIVITY OF THE BLOOD IN GLYCOSURIA

Glycosuria may be divided into four groups:

- (a). La pique of Claude Bernard.
- (b). Alimentary glycosuria.
- (c). Phloridzin diabetes.
- (d). Pancreatic diabetes.

(a). Claude Bernard, the originator of la pique, has shown unquestionably the relation of injury of a group of medulla cells to glycosuria. This type is unobtainable in a starving animal and is entirely dependent on glycogenolysis. It has been attributed to sudden flushing of the liver with blood, causing a rapid conversion of glycogen

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1. Meyers and Killian: Jour. Biol. Chem. 29:179, 1917.

to sugar. It may be due to a sudden activation of diastase in the blood, from some source or other, stimulated by the injury to the nerve tissue; or to a lowering of the threshold of excretion of sugar in the kidneys.

Much remains to be said about hyperglycemia in this type of glycosuria.

(b) Alimentary glycosuria is frequent in its occurrence, appears with an intestinal stasis and toxemia with poor oxidation, and disappears on correction of these ailments. It may exist with quite normal kidneys with a glycemia of but 150 to 200 mg. of dextrose per 100 c.c. of blood, and in nephritis the dextrose may arrive at a concentration of 200 to 400 mg. before it begins to be excreted, depending on the severity of the renal lesion. It is possible that putrefaction products in constipation cause an inhibition of glycogenesis or a much inhibited sugar utilization. Further investigation of ferment activity is needed to throw light on this subject.

(c) Phloridzin diabetes, purely an experimental type, suggests only the changes possible in the permeability of renal cells to different blood factors, and adds strength to the much discussed question of selective retention of the various products normally excreted by the kidneys from the blood.

Loewi² believes that it converts colloidal blood sugar into diffusible blood sugar, resulting in an immediate diffusion through the renal cells, which are unaffected by the phloridzin. Stiles and Lusk³ have shown that dextrose, uniting with the colloidal radical in the blood, is not burned, and that dextrose injected subcutaneously reappears in the urine. On the other hand, Rosenfeld and Asher⁴ find blood sugar readily diffusible. Therefore, the action of phloridzin must be in increasing the permeability of the renal cell membranes, rather than in altering the chemical state of the sugar.

To digress somewhat on the subject of phloridzin glycosuria, consider for a minute the question of permeability of membranes and the important bearing it must have on carbohydrate metabolism. The carbohydrates of the food are absorbed into the portal circulation as a monosaccharid, and some of this is stored as the polysaccharid, glycogen, in the liver. A portion not stored here is deposited in the muscles also as glycogen; a part of it is utilized immediately by the tissues for work and heat; some glucose remains in the blood stream for the maintenance of the normal concentration of sugar in the blood. Normally, on absorption of sugar there is an immediate stimulus to storage of this material in the tissue cells. The so-called "stimulus" must be merely a mechanical factor of the fluid on the outside of the

2. Loewi: Arch. f. exper. Path. u. Pharmacol. 48:410, 1902.

3. Stiles and Lusk: Science of Nutrition, p. 274.

4. Rosenfeld and Asher: Zentralbl. f. Physiol. 14:449, 1905.

cell membranes becoming hyper-isotonic to the fluid inside, and the membrane being wholly permeable to sugar admits it until the fluids are again isotonic, or in balance. This process is shortened by the burning of some of the sugar, and the time covered by the entire procedure is two to three hours, when the normal level of the blood sugar is reached. At the moment this occurs, a reverse process begins. The blood sugar continues to be burned, which makes the blood hypo-isotonic to the cell fluid and osmosis reverses, with active glycogenolysis, until food ingestion adds a fresh supply of sugar to the blood. There is then a constant flow of sugar molecules either into or out of the cell, with possibly other substances permeable through this membrane.

With a persistent hyperglycemia and no glycogen storage, there undoubtedly is some change in the cell membrane which converts it to a membrane semipermeable to sugar and prevents its storage.

In phloridzin diabetes the renal cell membrane must undergo some change which, on the other hand, converts it from a semipermeable to a perfectly permeable membrane.

In alimentary glycosuria the hyper-isotonic state of the sugar of the blood to that of the tissue cells raises considerable osmotic pressure, which may stimulate the renal cells so that sugar is excreted. The point of osmotic tension at which glycosuria commences varies with the individual, and depends considerably on the state of the kidney and whether it is normal; so that in varying degrees of nephritis, the osmotic pressure of the sugar in the blood must rise higher in order to have a glycosuria. The patient begins to excrete sugar as soon as the threshold of excretion of that material is reached. He also responds with exactness to restriction of carbohydrates in his diet until the sugar in his blood becomes normal, when there is once more a normal balance in glycolysis and glycogenolysis and a distinct relief of the irritating high osmotic pressure on the renal cells. This relieves the irritating symptoms of polyuria so common to glycosuria, and especially in chronic interstitial nephritis.

The question resolves itself into what can change the permeability of a membrane? The agent in the blood that does this cannot be incorporated in fixed tissue cells, but must be an internal secretion carried by the blood. All tissues contain diastase, but not all of them contain activators of this ferment. The one tissue which we know contains both is the blood.

(d). Pancreatic diabetes has long been a subject of research, and we are little farther advanced than Claude Bernard left us in 1856. Von Mering and Minkowski,⁵ in 1892, proved that the depancreatized

5. Von Mering and Minkowski: Arch. f. exper. Path. u. Pharmacol. 26:371, 1890.

dog has an extreme diabetes; while if a piece of pancreas be ingrafted under the skin of the dog, he remains sugar-free for two months, but on extirpation of the graft, diabetes is precipitated and the dog dies.

It has been generally conceded that the pancreas has an internal secretion that controls carbohydrate metabolism; and Baumel, Lemaire and Lannois, Lepine and Audry with several other observers are satisfied that the Islands of Langerhans in the pancreas are the secreting cells of its internal secretion.

DeMeyer⁶ shows that the liver from a depancreatized animal, perfused with Ringer's solution can have storage of glycogen function restored by adding pancreatic extract. He does not say whether the addition of any other glandular extract will be similarly effective. Von Mering and Minkowski have shown that diabetes is not a nerve lesion; nor an alteration of liver function through impaired circulation; nor an impairment of digestion of carbohydrates.

Harley⁷ assures us that the glycosuria is not due to injury of the nerves of the celiac plexus, but solely to "total arrest of pancreatic function," and adds that the entire pancreas, rather than the islands alone, plays the part.

Pathologists agree on the findings in diabetes.

Cecil,⁸ in 1908, reported very completely ninety cases of diabetes with pathologic-anatomic studies, and found that 79 per cent. of these cases had definite anatomic changes in the islands. Of these, 40 per cent. had a moderate sclerosis and 35 per cent. advanced sclerosis. Lydia DeWitt,⁹ in a large series of cases, observed that the Islands of Langerhans contain more connective tissue with advancing age — but this is characteristic of all parenchyma.

Cecil⁸ mentions one case in particular with marked pancreatic lipomatosis coming to necropsy. There had been no diabetes, yet only a small fraction of the parenchyma survived; which, however, compensated for the lost tissue in being very rich in well preserved Islands of Langerhans.

The islands in diabetes are found to be surrounded by thick fibrous sheaths. The fibrillary coating of insular capillaries is definitely increased in thickness, converting vessels to coarse septa which extend in from the capsule and anastomose at the center of the interacinar island. The cells forming the column show little change.

Considerable study has been made of other internal secreting organs with a view of finding a possible different source of material

6. DeMeyer: *Arch. de physiol.* 1909-1910, pp. 1-100.

7. Harley: *Jour. Anat. and Physiol.*, London 26:204, 1891-1892.

8. Cecil (two papers): *Med. and Surg. Rep. Presb. Hosp.*, New York 8:173 and 217, 1908.

9. DeWitt: *J. Exper. Med.* 8:193, 1906.

controlling carbohydrate metabolism. Cecil⁸ thought of this and mentions several cases of changes in the pituitary gland besides sclerosis of the Islands of Langerhans in diabetes. With stimulation of adrenals by way of the sympathetic nerves, MacKenzie¹⁰ found that glycogenolysis increased, and there was a hyperglycemia. It does not, however, cause a loss of glycolytic activity which is part of the altered metabolism in pancreatic diabetes. On extirpation of the adrenals in depancreatized dogs, the hyperglycemia disappears. There is no definite relation between the adrenal medulla and the Islands of Langerhans.

It is accepted that insufficient activity of the Islands of Langerhans will cause diabetes, but there are several other factors that may cause it, about which we as yet know nothing.

There are no records of the frequency of cirrhosis of the pancreas in syphilitics, but judging from the rapidity with which cirrhosis of all parenchyma occurs in this disease, it is not difficult to assume that the pancreas likewise suffers.

Warthin and Wilson,¹¹ Laignel¹² and Antoine¹³ reported a relative frequency of the presence of syphilis in diabetics, but nothing has been said of the alteration of the blood chemistry in this type of case. The syphilitic diabetic is either diabetic because of his syphilis, or made much worse by it, and unquestionably the syphilitic diabetic has a much greater involvement of the Islands of Langerhans than the nonsyphilitic diabetic.

The diastatic activity of the blood of the ordinary syphilitic varies as normally; in the simple diabetic the diastatic activity is extremely high, ranging from 40 to 100, usually around 60 or 80, as Meyer and Killian¹ also noted. But without exception those diabetics who are syphilitic have a low diastatic activity, while both types have varying degrees of hyperglycemia.

Each of the five syphilitic diabetics in our records had a notably low carbohydrate tolerance, and we have thus far been unable to get a syphilitic diabetic under sufficiently long observation to state whether his increased tolerance rises to normal after the syphilis is cured, or whether some permanent ferment injury has been done. In one case, however, the patient came into the hospital with diabetes and gangrenous foot, improved rapidly in health and the foot healed after two arsphenamin treatments, and his carbohydrate tolerance almost doubled.

10. MacKenzie, G. M.: *Arch. Int. Med.* **19**:593, 1917.

11. Warthin and Wilson: *Am. J. Med. Sc.* **152**:157, 1916.

12. Laignel: *Rev. neurol., Paris* **22**:481, 1914.

13. Antoine: *Arch. méd. d'angus* **17**:147, 1913.

The syphilitic diabetic has the most extreme loss of carbohydrate tolerance, which, it is our personal belief, will be checked on cure of the syphilis, if the patient is given the same dietetic care that any diabetic should receive, keeping the hyperglycemia reduced to normal.

If it is possible to have a low diastatic activity and diabetes, then the disease does not depend solely on glycogenolysis, but may be due to the failure of the tissues to hold or to burn sugar.

It seems incredible that the Islands of Langerhans should secrete an activating agent for diastase that sometimes activates and sometimes inhibits; but this must be true if we accept the idea that pancreatic diabetes and syphilitic diabetes have the same cause — insufficiency of the secretion of the Islands of Langerhans — for in one case the diastatic activity is very high and in the other low. The only explanation we can offer for this is that the Islands of Langerhans secrete a substance inhibitory to the action of diastase, and thereby control its activity. If this is true, then the increased diastatic activity in pancreatic diabetes is due to destruction of the islands so great that there is no inhibiting agent of diastase secreted, and the diastase in the blood is superactive.

In the syphilitic diabetic, cirrhosis is not confined to the islands of the pancreas, but involves all parenchymatous tissue. This encroaches on the secreting cells which, in turn, are irritated and stimulated to excessive secretion. The diastase is inhibited to a greater degree, with resultant low diastatic activity. One never finds increased diastatic activity with a hypo- or normal glycemia, but it is not uncommon to find hyperglycemia and a low diastatic activity. So we conclude that the hyperglycemia of diabetes is due to another cause than increase of glycogenolysis alone, and it probably is something affecting the permeability of cell membranes to sugar and inhibition of glycolysis, so that all the sugar remains in the blood, to be excreted, or a very small portion burned.

Table 1 gives data of seventeen cases, of which six patients are syphilitic. Of these six, only one was suspected of having syphilis; the other five were well symptomatically, with the exception of their diabetes. Each case of simple diabetes shows the greatly increased diastatic function and hyperglycemia, and the syphilitic diabetics are characterized especially by their hyperglycemia and low or normal diastatic function. Several of the nonsyphilitic diabetics are somewhat atypical, with high sugars and not excessively active diastatic functions.

Case 2, for instance, was a business man, exhausted by the long strain of an exacting business. With a complete rest and tolerance dieting, he made a complete recovery and now has a normal blood chemistry and tolerance for carbohydrates.

Case 4, a woman with a history of diabetes and deafness for four years, had a tolerance of 30 gm. of carbohydrates at the time the blood was taken, and was very weak. Improvement was striking with antisyphilitic treatment.

Case 1 was a ward patient brought in for gangrenous foot. He was given arsphenamin, and the foot healed uneventfully. The carbohydrate tolerance in this case increased from 35 gm. to 60 after the arsphenamin.

TABLE 1.—DIABETICS.

Case	Sex	Age	Diagnosis	Wasser- mann	Blood Sugar, Mg. per 100 C.c.	Diastatic Function
1	♂	60	Diabetes.....	+++	400	20*
2	♂	48	Diabetes.....	Neg.	298	38
			One month of rest and diet.....	Neg.	150	38
3	♂	28	Diabetes.....	+++	200	10*
4	♀	36	Diabetes.....	+++	400	25*
5	♀	65	Diabetes.....	Neg.	334	66
6	♂	60	Diabetes.....	Neg.	349	69
7	♀	60	Diabetes.....	+++	400	20*
8	♂	46	Diabetes.....	Neg.	405	75
9	♂	40	Diabetes.....	Neg.	435	113
10	♀	40	Diabetes.....	Neg.	400	102
11	♀	45	Diabetes and nephritis.....	+++	421	5*
12	♂	40	Diabetes.....	Neg.	400	44
13	♂	50	Diabetes....	Neg.	266	46
14	♂	51	Diabetes.....	++	191	25*
15	♀	55	Diabetes.....	Neg.	261	62
16	♂	60	Diabetes (cancer).....	Neg.	266	79
			Half hour later.....	Neg.	266	60
			Day later.....	Neg.	500	60
17	♂	61	Diabetes.....	Neg.	235	33

* Syphilitic.

Case 16 was a cancer patient with diabetes. His blood chemistry study was made before roentgen-ray treatment, one half hour after, and twenty-four hours after. The great increase in blood sugar on the day following the roentgen-ray treatment was due not to the roentgen ray, but to an excessive carbohydrate ingestion.

Case 17 is similar to Case 2. In this instance the patient had what his doctor called an alimentary glycosuria. His blood sugar increases only during periods of fatigue and his diastatic function remains normal.

Case 9 had been kept well below his tolerance of 75 gm. of carbohydrate, no glycosuria and with normal blood sugar for two years.

TABLE 2.—TUMOR CASES WITH ROENTGEN-RAY TREATMENT

Case	Sex	Age	Diagnosis	Wassermann Reaction	Sugar, Mg. per 100 C.c.			Diastatic Activity		
					Before X-ray	Half Hour after X-ray	Day after X-ray	Before X-ray	Half Hour after X-ray	Day after X-ray
1	♂	50	Postoperative epithelioma of penis for 6 months; living.	Neg.	142	190	235	11	42	31
2	♀	60	Epithelioma little finger, 13 years; improved.	Neg.	222	210	181	28	30	22
3	♂	..	Epithelioma of face.	Neg.	256	178	111	29	14	11
4	♂	34	Four months abdominal tumor; living.	Neg.	222	200	68	28	17	17
5	♂	21	Sarcoma foot	Neg.	171	222	200	65	12	10
6	♀	65	Two years carcinoma left breast; living.	Neg.	261	250	247	28	17	36
7	♂	34	Ten months adenocarcinoma cecum; well.	Neg.	333	337	166	47	13	33
8	♂	35	Angioma lower lip, cured.	Neg.	266	250	142	47	22	15
9	♂	52	Three months epithelioma left face.	Neg.	182	182	175	20	30	28
10	♂	54	Sarcoma left neck, 1 year; living.	Neg.	190	200	153	31	32	58
11	♀	57	Carcinoma left breast, 1 year; died.	Neg.	133	142	200	11	12	10
12	♂	65	Epithelioma left face, 30 years; living.	Neg.	160	114	153	8	8	28
13	♂	37	Melano sarcoma left groin, 1 year; died.	Neg.	135	427	137	38	86	12
14	♀	51	Epithelioma of vulva; living.	Neg.	133	100	118	38	50	21
15	♀	52	Epithelioma of vulva, 2 years; unimproved.	Neg.	173	160	113	20	31	18
16	♀	51	Carcinoma right breast, 18 months; improved.	Neg.	151	143	153	13	21	23
17	♀	52	Carcinoma left breast, 20 years; living.	Neg.	182	121	100	13	14	37
18	♂	71	Carcinoma bladder	Neg.	113	124	133	10	6	25
19	♂	59	Lymphosarcoma of right tonsil, 1 year.	Neg.	108	151	127	16	49	54
20	♂	57	Epithelioma left ear, 5 years; unimproved.	Neg.	112	153	260	51	48	17
21	♀	63	Epithelioma nose, 2 yrs.; clinically well.	Neg.	125	140	178	28	62	14
22	♂	16	Epithelioma lower lip, 1 year.	Neg.	113	113	113	21	3	9
23	♂	82	Epithelioma of nose, 10 months; unimproved.	Neg.	104	106	133	18	70	40
24	♂	64	Epithelioma right eye, 52 years; unimproved.	Neg.	188	181	154	31	13	26
25	♀	11	Carcinoma of cervix, postoperative, 5 months; living.	++	164	181	166	41	17	44
26	♀	40	Carcinoma of right breast, operation, recurrent, 4 years; died.	Neg.	171	163	87	41	18	47
27	♀	52	Carcinoma of uterus, 1 year; died.	Neg.	166	166	153	47	31	49
28	♂	16	Leukoplakia on mouth, 1 year; living.	Neg.	68	84	..	63	15	..

He had been able to do hard work in a steel mill during this time, and an attack of influenza temporarily broke his tolerance, when the blood study was made. It is steadily improving now, however, and the carbohydrate tolerance is picking up.

We studied twenty-nine cases of malignancy and the effect of roentgen ray on their blood chemistry (Table 2). We are utilizing the data of the sugar and diastatic function here, and the other studies are to be reported later.

The cancer patient shows no special feature of carbohydrate metabolism. There is a tendency to hyperglycemia, but in every instance this is due to the high carbohydrate diet these people had been getting, together with lack of exercise. The bed patient invariably shows deficient oxidative powers. The cancer patients studied were being treated with the roentgen ray, and the blood was obtained before exposure, one-half hour after and twenty-four hours after. Of the cases studied, several patients had slight renal lesions; but the majority were normal as to blood chemistry: 7 cases had hyperglycemia; 21 had normal sugar before roentgen ray; 13 had sugar increased one-half hour after; 15 had decreased one-half hour after; 9 had increased the day after; 19 had decreased the day after.

Those cases in which the sugars were lowest following roentgen ray treatment had received the largest doses, so we can say that the roentgen ray certainly increases oxidation of blood sugar, but this is true of any individual whether he has a malignant disease or not. In half of the cases the diastatic activity had increased one-half hour after roentgen-ray treatment, and in the rest there was a decrease. On the day following roentgen-ray exposure the diastatic activity of half of the cases studied had increased, and in the rest it had decreased. As the diastatic activity of patients treated with the roentgen ray under similar conditions did not show a consistent increase or decrease either one-half hour after or the day after roentgen-ray treatment, we can say that the rays have no special or permanent effect on the diastatic activity of the blood.

In the fifty-two miscellaneous malignant cases recorded in Table 3 the blood sugar varies with the diet and exercise of the patient. The diastatic function has no special relation to any condition that could be considered specific or diagnostic for malignancy.

Those syphilitics with the additional disease of cancer do not necessarily have a low diastatic activity. On the other hand, many of the nonsyphilitic cases have extremely low diastatic activities.

Sixty-one miscellaneous cases (Table 4) show very much the same thing in their blood chemistry as regards the sugar and diastatic activity that the cancer cases show.

TABLE 3.—CANCER CASES NOT ROENTGEN-RAYED

Case	Sex	Age	Diagnosis	Wasser- mann Reac- tion	Blood Sugar, Mg. per 100 C.c.	Dias- tatic Func- tion	Dura- tion	Present Condition
1	♀	48	Myoma.....	++	166	17	1 yr.	Died
2	♂	70	Epithelioma of face.....	Neg.	166	18	1 yr.	Died
3	♀	60	Carcinoma right breast.....	Neg.	250	30	5 yr.	Died
4	♂	27	Syphilis; granuloma.....	+++	260	30	14 mo.	Clinically well
5	♂	50	Epithelioma right cheek....	Neg.	188	38	2 yr.	Well
6	♀	36	Carcinoma uterus.....	+++	274	25	5 mo.	Died
7	♂	63	Papilloma bladder.....	Neg.	148	26	3 yr.	Unimproved
8	♀	39	Postoperative carcinoma cervix	Neg.	200	40	12 yr.	Unimproved
9	♀	65	Carcinoma breast.....	Neg.	118	23	2 yr.	Died
10	♀	61	Epithelioma nose.....	Neg.	160	26	1 yr.	Well
11	♀	61	Postoperative, recurrent carcinoma left breast	Neg.	117	7	7 mo.	Died
12	♂	41	Epithelioma lower gum.....	Neg.	153	22	6 mo.	Unimproved
13	♂	41	Epithelioma lip, lower.....	Neg.	130	40	4 yr.	Unimproved
14	♂	57	Epithelioma ear, left.....	Neg.	133	28	5 yr.	Living
15	♀	53	Carcinoma (colloid) rectum	Neg.	153	26	1 yr.	Living
16	♂	18	Epithelioma right upper jaw	Neg.	129	16	6 mo.	Died
17	♀	52	Carcinoma uterus.....	Neg.	153	19	1 yr.	Died
18	♀	49	Carcinoma uterus.....	Neg.	123	25	9 wk.	Living
19	♀	49	(8/14/18) (8/24/18)	136	14		
20	♀	49	(7/12/18)	117	31		
21	♀	62	Epithelioma shoulder, left..	Neg.	235	47	30 yr.	Unimproved
22	♀	55	Melanosarcoma Achilles tendon	+	160	48	6 yr.	Operated; well
23	♀	65	Carcinoma esophagus.....	Neg.	181	44	1 yr.	Living
24	♂	49	Syphilis and epithelioma soft palate	+++ (10/4/18)	190	50	4-5 mo.	Died
25	♂	49	(8/21/18)	118	40		
26	♀	51	Carcinoma cervix.....	Neg.	172	38	1 yr.	Died
27	♀	42	Round cell sarcoma.....	Neg.	166	66	1 yr.	Living
28	♂	80	Carcinoma bladder.....	Neg.	400	80	1 yr.	Living
29	♀	45	Carcinoma stomach.....	Neg.	286	76	4 mo.	Died
30	♀	60	Epithelioma tongue.....	Neg.	166	46	6 mo.	Untreated
31	♀	61	Pyloric ulcer, obstruction...	Neg.	154	39	all life	Living
32	♂	53	Mediastinal tumor.....	Neg.	285	23	3 mo.	Unimproved
33	♂	39	Carcinoma of breast.....	Neg.	250	30	2 yr.	No recurrence
34	♀	60	Epithelioma finger, left hand	Neg.	202	15	13 yr.	Improved
35	♀	39	Carcinoma cervix.....	++	166	47	6 mo.	Clinically well
36	♀	45	Carcinoma cervix.....	+	187	30	4 yr.	Improved
37	♀	59	Lymphosarcoma, probable primary in tonsil	Neg.	178	25	18 mo.	Unimproved
38	♀	43	Adenocarcinoma uterus.....	Neg.	235	19	10 yr.	Living

TABLE 3.—CANCER CASES NOT ROENTGEN-RAYED—(Continued)

Case	Sex	Age	Diagnosis	Wasser- mann Reac- tion	Blood Sugar, Mg. per 100 C.c.	Dias- tatic Func- tion	Dura- tion	Present Condition
39	♀	76	Epithelioma vulva.....	Neg.	149	44	8 mo.	Living
40	♀	51	Carcinoma ovary.....	Neg.	181	21	2 yr.	Living
41	♂	62	Gumma (bridge of nose)...	Neg. (10/15/18)	166	24	1 yr.	Living
42	♂	(10/22/18)	244	16		
43	♂	(11/ 9/18)	181	64		
44	♂	74	Epithelioma epitrochlear region, prickle cell	+	244	31	5 mo.	Living
45	♀	29	Carcinoma uterus.....	Neg.	200	40	7 mo.	Unimproved
46	♀	52	Sarcoma of neck.....	++	181	36	4 mo.	Clinically well
47	♂	57	Epithelioma branchial re- mains	++	142	24	4 mo.	Unimproved
48	♀	34	Angioma eye.....	Neg.	166	15	32 yr.	Living
49	♀	66	Carcinoma uterus.....	Neg.	181	44	4 yr.	Improved
50	♀	31	Splenic anemia.....	Neg.	285	23	1 mo.	Unimproved
51	♀	65	Epithelioma of nose.....	Neg.	200	40	1 yr.	Well
52	♂	..	Epithelioma of scrotum....	Neg.	250	50	5 yr.	Died

TABLE 4.—MISCELLANEOUS CASES

Case	Sex	Age	Diagnosis	Wasser- mann	Blood Sugar, Mg. per 100 C.c.	Diastatic Function
1	♂	55	Nephritis.....	Neg.	298	40
2	♂	25	Nephritis.....	Neg.	105	41
3	♀	42	Nephritis.....	Neg.	181	97
4	♂	50	Nephritis.....	Neg.	202	39
5	♂	50	Nephritis.....	++	148	27
6	♂	45	Nephritis.....	Neg.	154	9
7	♀	55	Nephritis.....	Neg.	142	9
8	♀	60	Nephritis.....	Neg.	87	22
9	♂	50	Nephritis.....	Neg.	259	17
10	♂	45	Nephritis.....	Neg.	250	8
11	♀	47	Nephritis.....	Neg.	175	26
12	♀	49	Nephritis.....	++	307	11
13	♀	55	Nephritis.....	Neg.	222	15
14	♀	52	Arthritis deformans.....	Neg.	223	27
15	♂	38	Arteriosclerosis.....	Neg.	164	39
16	♂	62	Depressive insanity.....	Neg.	333	33
17	♂	27	Hemorrhagic retinitis.....	Neg.	200	40
18	♂	38	Hemorrhagic retinitis.....	Neg.	111	26
19	♂	30	Hemorrhagic retinitis.....	Neg.	181	16
20	♂	38	Exophthalmic goiter.....	Neg.	250	30
21	♀	34	Exophthalmic goiter.....	Neg.	185	30

TABLE 4.—MISCELLANEOUS CASES—(Continued)

Case	Sex	Age	Diagnosis	Wasser- mann	Blood Sugar, Mg. per 100 C.c.	Diastatic Function
22	♀	34	Exophthalmic goiter.....	Neg.	140	25
23	♀	34	Exophthalmic goiter.....	Neg.	166	44
24	♀	34	Exophthalmic goiter.....	Neg.	80	13
25	♀	34	Nervous and tired.....	Neg.	154	60
26	♂	45	Nervous and tired.....	Neg.	285	49
27	♀	55	Nervous and tired.....	Neg.	143	35
28	♀	55	Nervous and tired.....	Neg.	250	50
29	♀	38	Nervous and tired.....	Neg.	192	51
30	♀	40	Nervous and tired.....	Neg.	166	24.8
31	♀	52	Pyelitis.....	Neg.	146	22
32	♀	36	Pyelitis.....	Neg.	143	24
33	♀	36	Epilepsy.....	Neg.	111	25
34	♂	65	Cardiorenal disease.....	Neg.	142	38
35	♀	60	Cardiorenal disease.....	Neg.	147	31
36	♂	38	Headache (autointoxication).....	Neg.	111	34
37	♂	41	Headache.....	Neg.	133	39
38	♀	48	Headache.....	Neg.	142	50
39	♂	55	Headache.....	Neg.	303	46
40	♂	40	Headache.....	Neg.	200	93
41	♀	45	Headache.....	Neg.	162	67
42	♂	30	Normal.....	Neg.	148	20
43	♀	56	Normal.....	Neg.	106	22
44	♂	53	Normal.....	Neg.	266	12
45	♀	27	Normal.....	Neg.	100	25
46	♀	23	Normal.....	Neg.	200	40
47	♀	25	Normal.....	Neg.	122	32
48	♀	25	Normal.....	Neg.	188	7
49	♀	25	Normal.....	Neg.	143	28
50	♂	60	Myocarditis.....	Neg.	166	24
51	♂	55	Tuberculous pleurisy.....	Neg.	133	52
52	♀	52	High blood pressure.....	Neg.	156	46
53	♂	35	Asthma.....	Neg.	145	36
54	♂	40	Prostate.....	Neg.	170	56
55	♂	45	Glaucoma.....	Neg.	156	22
56	♂	40	Glaucoma.....	Neg.	290	92
57	♀	50	Rheumatism.....	Neg.	166	47
58	♂	32	Rheumatism.....	Neg.	121	27
59	♀	50	Uleer stomach.....	Neg.	154	49
60	♀	62	Tingling in fingers.....	Neg.	166	24
61	♂	35	Ureteral stone.....	Neg.	290	16

The nephritics have a retention of sugar depending on the severity of their lesion. The diastatic activity varies as in health.

In the case of arthritis deformans the patient had a general retention which was entirely corrected by diet.

The depressive insanity patient had a blood sugar of 333 and no glycosuria; it was probably due to diet and restraint in bed, and in his kidneys a high threshold of excretion for sugar.

The cases of hemorrhagic retinitis and glaucoma gave moderately increased blood sugars, and in one case, No. 56, an enormously increased diastatic activity.

Exophthalmic goiter cases gave high blood sugars, and indefinitely varying diastatic activity. Patients with pyelitis, cardiorenal lesion, epilepsy, myocarditis, tuberculous pleurisy, asthma, hypertrophied prostate, rheumatism and ulcer of the stomach, have normal blood sugar and normal diastatic activity.

The group of persons having no symptoms but those of overwork show a lack of oxidation of their sugar and at the same time a high diastatic activity. This may be traceable partly to an accumulation of unoxidized materials in the blood.

Eight normal persons were studied and each had normal blood chemistry, with the exception of two whose high blood sugar was purely dietary.

The blood sugar and diastatic activity are very variable, and up to the present their chief value lies in their definite relation to diet.

In our work we have had an opportunity to study nine eclamptics carefully (Table 5), and in this series there were no syphilitics. Glycosuria and hyperglycemia during the latter months of pregnancy are very frequent. These cases show only a moderate hyperglycemia, although it is at a time in pregnancy when one would expect the blood sugar to be much higher.

TABLE 5.—CASES OF PREGNANCY

Case	Sex	Age	Diagnosis	Wassermann	Blood Sugar, Mg. per 100 O.c.	Diastatic Function
1	♀	28	Eclampsia.....	Neg.	200	42
2	♀	27	Pernicious vomiting.....	Neg.	181	30
3	♀	29	Eclampsia.....	Neg.	165	27
4	♀	30	Eclampsia.....	Neg.	142	11
5	♀	28	Eclampsia.....	Neg.	184	20
6	♀	20	Eclampsia.....	Neg.	167	38
7	♀	26	Eclampsia.....	Neg.	160	25
8	♀	25	Eclampsia.....	Neg.	160	16
9	♀	26	Eclampsia.....	Neg.	125	25

The diastatic activity is normal in all except the first woman, who had a marked glycosuria.

The blood sugar and diastatic function behave very much as in the normal individual—affected by diet or renal insufficiency, but nothing else that is demonstrable in these few cases.

CONCLUSIONS

1. There is a low diastatic activity in diabetes associated with syphilis.

2. The internal secretion of the pancreas is probably inhibitory to the activity of the diastase in the blood.

3. Exposure to roentgen rays for either long or short periods of time does not alter the activity of the diastase, but in some cases temporarily lowers the sugar content of the blood.

4. There is nothing especially characteristic of either the blood sugar or diastase of the cancer patient at any stage of his disease.

5. Miscellaneous nondiabetic cases show normal sugar in the blood with normal or low diastatic activity; or high sugar with increased or low diastatic activity; but never low sugar with high diastatic activity.

6. The diastatic activity tends to increase with rising sugar in the blood, especially with a dietary glycemia.

7. In dietary correction of a hyperglycemia the diastatic activity decreases with the sugar, whether in a diabetic or not.

Further studies on the problem of diastase are in progress.

FATIGUE DISEASE

AS EXEMPLIFIED IN FUNCTIONAL DISORDERS OF THE STOMACH AND
THYROID GLAND *

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The absorption and utilization of nutriment by a voluntary muscle is evidently dependent on the impulse conveyed in its motor nerve. Without that impulse, as after section and degeneration of the nerve, the muscle atrophies. The impulse, of course, performs its function, which thus must be, at least in part, trophic, at the distal extremity of the nerve or its end-plate. This, when the trunk of the nerve has been irritated by repeated electric shocks, can be readily made to cease functionation because of fatigue. When its onset is indicated by the decreasing contractions of the muscle, the intravenous injection of extracts of the thyroid, parathyroid and adrenal glands will immediately reinvigorate the failing contractions.¹ If, however, the fatigue of the end-plate is carried to the point of exhaustion, then these extracts become inert. In other words, the thyroid, parathyroid and adrenal glands probably pour into the circulation some material which produces a stimulating effect on the voluntary muscles through the intermediation of the nerve impulse at its point of discharge, or the motor end-plate. After the latter is destroyed, or ceases to functionate, neither food nor material derived from the thyroid, parathyroid or adrenal glands seems able to gain access to the muscle.

Unstriated, or involuntary muscle, as represented in the cat's uterus and different portions of the intestine, are believed to have a double nerve supply from the involuntary system. Irritation of one portion of this system produces contraction, and of the other relaxation. These contractions can be stimulated by extracts of several organs, including the thyroid and parathyroid glands. After the contractions have been thus started, they can be immediately inhibited or paralyzed by a 1:1,000 solution of epinephrin chlorid. The latter is accepted as having a selective stimulant effect on the terminal filaments of the sympathetic, and, therefore, because of its antagonistic action to the stimulating extracts, it is probable that the thyroid, parathyroid

* This article represents lectures delivered before the West Virginia State Medical Association, Oct. 2, 1918, and the Bellevue Hospital Alumni Association, Nov. 6, 1918.

1. Am. J. Physiol. 45:97 (Jan.) 1918.

and other organs produce their effect through either the terminals of the sympathetic or its opponent, the vagus system.²

It should be recalled that the involuntary nervous system, as noted, is composed of two parts, or groups, of nerves, and fibers from each are believed to supply every organ in the body except, so far as is known, the brain. This double innervation of all viscera apparently represents a regulating mechanism for controlling their interactivity. One set of fibers seems in general to activate the receiving cells, while the other, with the same distribution, inhibits them and, at the same time, produces vasoconstriction. The "activating" group, which may also contain vasodilating parts, is carried in the third, seventh, ninth, tenth and eleventh cranial nerves, and in the visceropelvic nerve (to the rectum, bladder and genitals), and has been designated by Langley as the autonomic system. It might be more easily identified under the name of its most prominent member, or as the vagus group or system. The inhibiting and vasoconstricting fibers are in the sympathetic with its cervical, thoracic and abdominal plexuses.

This double and apparently opposing or counteracting nerve supply of the viscera is most easily demonstrable in the stomach, in which the peristalsis and secretion are increased by electrical stimulation of the vagus, while both processes are inhibited by similar stimulation of the splanchnics. These same reactions can be excited in a more vigorous form and over a longer period by materials obtained from certain organs. That is, the subcutaneous injection (in dogs) of an alcohol extract, or of the noncoagulable part of a saline extract, particularly of the thyroid or parathyroid glands and of one or two other organs, or an acid decoction of the pyloric mucosa of the stomach (gastrin), will greatly stimulate the flow of gastric secretion. Extracts of the thyroid will increase this flow from five to ten times the normal amount, and decidedly increase the content of hydrochloric acid and the gastric peristalsis. The injection of atropin, which paralyzes the terminal filaments of the vagus, prevents or inhibits these (thyroid) reactions. The injection of a 1:1,000 solution of epinephrin likewise prevents or inhibits the stimulation by the thyroid and other organ extracts; but its action must be, as in the paralysis of the involuntary muscle contractions, through stimulation of the opponent of the vagus, or the terminal fibers of the gastric sympathetic, because epinephrin acts only on the sympathetic. This inhibition of the stomach activity apparently by the adrenal gland cannot be ascribed to the power of epinephrin to cause vasoconstriction, because none can be detected, and also because the adrenal nucleoprotein material which contains

2. *Am. J. Physiol.* 39:154 (Dec.) 1915.

only traces of epinephrin, is very much more active than corresponding doses of epinephrin chlorid solution.

After both vagi are cut just above the diaphragm the quantity of the gastric secretion becomes reduced to about one-tenth of the normal, the stomach gradually dilates and is unable to empty itself, and the animal eventually dies, apparently of inanition. Before the general condition becomes bad, the injection of thyroid (and certain other stimulant organ) extracts is followed by practically no increase in the gastric secretion, but what little flow there is, is checked, as in the normal stomach, by the injection of epinephrin or of derivatives of the adrenal gland. That is, the stimulant extracts do not act, but the adrenal products still show their vigorous inhibiting power when the vagus has been destroyed and only the sympathetic is intact. Extracts of the pituitary show inhibitory effects which are similar to but less vigorous than those from the adrenal, and probably also act through the sympathetic, although this has not been definitely determined.³

All of the stimulant organ products, except possibly gastrin, seem thus to have an affinity for the terminal filaments of the gastric vagus and to intensify its apparent function. The products of the adrenal gland, on the other hand, and possibly also of the pituitary, have an affinity for, and intensify the apparent inhibitory power of the gastric sympathetic terminals.

Of all the functional disorders, those which involve the stomach and the thyroid gland are probably the most common, and they present many analogies and similarities. Each organ is supplied by the vagus and the sympathetic, each is subject to under- or overactivity and presumably to the same inhibiting and activating influences and their probable trophic accompaniments. Clinically, moreover, the corresponding functional disturbances in these organs occur and are intensified or relieved under the same general conditions in the same general type of "nervous" individuals.

A "nervous" person can be defined as one who responds to all stimuli with more than the usual rapidity and expenditure of energy, and in these responses, which are necessarily through the nerve terminals, fatigue should affect not only the motor end-plates, but also the involuntary or visceral nervous system. The latter is presumably subject to the same laws as the voluntary nerves, and though a fatigue and consequent defect or failure in functionation of the terminals of the gastric vagus or sympathetic has not been definitely proved, there can be little doubt of its occurrence. Certainly, if the experimental animal is angered or terrified, which is an emotion akin to worry, the

3. *Am. J. Physiol.* 39:345, 1916; *Ibid.* 48:79 (Feb.) 1919.

flow of its gastric secretion immediately ceases, and this has been proved to occur by inhibitory impulses conveyed to the stomach through its sympathetic nerve supply. When these impulses are long enough continued, the sympathetic terminals should suffer from a partial or complete fatigue failure, and the vagus would then be left to functionate without opposition. The result should be hypersecretion, hyperacidity and hypermotility or pylorospasm. These conditions are frequently encountered in nervous persons who have been subjected to fatigue and worry, and they are relieved by rest, presumably to permit the exhausted sympathetic terminals to regain their capacity to functionate. The usual medical treatment is by belladonna, which, of course, paralyzes the terminals of the apparently overactive vagus (although it is probably only unopposed), and by alkalis which, theoretically, at least, are more logical. For it is not impossible that alkalis, by neutralization of the excess of hydrochloric acid, prevent the formation of gastrin and a consequent autoactivation of the stomach.

As derivatives of the adrenal gland, experimentally, show vigorous gastric inhibition, their administration is logical. The most active of these products seems to be the nucleoprotein material. This can be obtained from an aqueous extract of the hashed fresh glands by precipitation with 10 per cent. acetic acid. The dose of the dried (nucleoprotein) powder is about 0.5 to 1 grain every two or three hours. Its effects are shown in the following rather abbreviated case history:

CASE 1.—F. H., aged 27, a hospital orderly of the pronounced nervous type, complains for the past ten years of recurrent attacks of epigastric pain and distress which always come on after a period of night duty, especially when the service is active. The pain is slightly relieved by gas eructations and by "soda." After a few days, or rather nights, of hard work and worry the pain increases and awakens him during his sleeping period. With day duty and comparative rest the pain gradually subsides. Ewald test meal, Aug. 27, 1918, shows total acidity of 89; free acid 58. The roentgen ray at this time revealed hyperperistalsis and probable pyloric ulcer. Rest in bed, with the usual dietetic and medical treatment, resulted in no subjective improvement.

Sept. 11, 1918. Ewald test meal showed total acidity 93; free acid 54. Restriction in diet was then abandoned, and 1 grain of dried adrenal nucleoprotein material was given by mouth every two hours.

Sept. 25, 1918. The Ewald test meal showed a total acidity of 62; free acid 50, and the symptoms had disappeared. The patient returned to day duty and continued the adrenal proteins but avoided the fatigue of night work and up to the present writing (three months) remains well.

The commercial desiccated adrenal powder, or the 1:1,000 solution of epinephrin are, clinically and experimentally, not as efficacious in relieving hyperacidity and pylorospasm as the adrenal nucleoprotein material.

If the disturbance is severe and lasts long enough, it is, of course, regularly followed by ulceration. There is reasonable certainty that

acute ulcers of the stomach can be caused by bacterial infection, but in spite of Rosenow's demonstration of specific cocci in chronic ulcers, there is still some doubt as to their etiologic relationship. Infection may begin the process, but the cause of its continuation is obscure. If, however, the normal activity and quiescence of the stomach are dependent, as they seem to be, on the integrity of the organ's double nerve supply in conjunction with the secretions or products of other viscera, then any interference with this relationship, like a fatigue failure of the gastric sympathetic, might be followed by a defect in nutrition which should be localized in the region of greatest anemia, or where the muscular contractions are most pronounced. Hence there is still some reason for suspecting that gastric ulcer may have a trophic origin.

The cause of the chief subjective symptom, or the pain of this condition, is generally conceded to be due to spasm and not to the irritation by food or hydrochloric acid of the exposed surface of the ulcer. This spasm is, of course, dependent on the activity of the vagus nerve, which, in all probability, is "active" not because of some pathologic condition of the vagus, but because of a failure in function by its physiologic opponent, or the gastric sympathetic. The cause of this greater or less amount of functional failure in the sympathetic terminals is most reasonably explained by fatigue. This seems to involve some trophic, or both trophic and inhibitory influence exerted by the combination of the nerve impulse with the adrenal and possibly other organ products. When this balanced innervation, with its "nutritional" accompaniment, becomes impaired, as by a fatigue failure of the sympathetic, the unopposed action of the vagus should and evidently does result in hyperacidity and pylorospasm. In the experiments noted above, "gastrin" (made by boiling the pyloric mucosa in 0.4 per cent. hydrochloric acid) stimulates the stomach like extracts of the thyroid, and, therefore, in the presence of an excess of hydrochloric acid and in the absence of the restraining influence of the sympathetic, the stomach theoretically, at least, becomes auto-activated. The "gastrin," which presumably is formed by the action of the excess of hydrochloric acid on the pyloric mucosa, returns in the circulation to its source and continues the stimulation of the vagus or the gastric epithelium. This supplies the most reasonable explanation for the relief of symptoms which follows the administration of alkalis or the usual gastro-jejunostomy with the admission to the stomach of the alkaline pancreatic secretion. But this operation, with its relief of hyperacidity, or when there is no hyperacidity, does not always cure the pain which presumably means spasm. The explanation of its persistence or later occurrence, especially when no ulcer is present, must indicate not necessarily a fault in the hypothesis of gastrin auto-

activation, but a continuation of the original functional failure of the sympathetic. If the pain is due to a pyloric spasm, it should then be relieved by a pyloroplasty or Finney operation.

The following case history is illustrative:

CASE 2.—W. J., aged 32, a mechanic, decidedly of the nervous type, underwent a gastro-jejunostomy in June, 1917, for pyloric ulcer, which was not excised. Thereafter, his symptoms disappeared for several months. A year later, after a period of unusually hard work under trying circumstances, the same epigastric pain gradually returned. It was intensified by food, especially meat, and for the last month awakened him at night. The Ewald test meal showed a total acidity of 47; no blood. The roentgen ray revealed a patent and functioning gastro-jejunostomy, through which the bismuth meal rapidly passed. There was hyperperistalsis and, apparently, pylorospasm.

Oct. 5, 1918, exploration showed a perfect posterior gastro-jejunostomy and no adhesions about it or the duodenum. The latter contained in its upper curvature a thickened area which was apparently the former ulcer.

A 4-inch gastroduodenostomy, or Finney's operation, was then performed and no ulcer found. The previous gastrojejunostomy was not disturbed. Recovery was uneventful and the former distressing pain ceased and has not since recurred.

If, therefore, the spasm can be localized with reasonable certainty in the pylorus, even when no ulcer exists, a wide division of the circular muscular fibers at this point, as can be done by a Finney operation, is a logical mechanical treatment and is applicable under the proper conditions even when no ulcer is found. Doubt of the existence of an ulcer is often embarrassing, and prevents many useful and necessary operations because, when the ulcer is not present, experience has proved that the results of the usual gastro-jejunostomy are disappointing, and a simple exploration may not be regarded as justifiable. Therefore, the Finney operation in these cases is extremely useful, and is indicated when the epigastric pain cannot be relieved by the usual medical treatment (with adrenal feeding and rest) and is of enough severity and duration to impair the patient's working powers.

Excision of the ulcer whenever possible has been proved to be always expedient, and its removal when in the body of the stomach by transverse resection of the viscus is also logical because of the resultant, at least partial, paralysis of the gastric vagus. The subsequent defective functionation of this nerve with the consequent decrease of hydrochloric acid formation and muscular contraction, should relieve the apparent overactivity certainly of the distal portion of the gastric vagus. The division of the stomach apparently does not cause the complete paralysis of the organ which takes place in the experimental animal after vagus section in the thorax.

Rodman's operation of excision of the ulcer-bearing area serves the same purpose as transverse resection, so far as the functions of

the gastric nerves are concerned, but more radically and with greater risk.

The symptoms, then, at least of chronic gastric ulcer, are those of gastric hyperfunctionation, and the ulcer seems merely an incident and, although the complications, consequences and treatment of the ulcer are very important, it is apparently not the primary essential lesion which may be, not only a lack of balance in the innervation of the stomach, but also a hypofunctionation on the part of the chromaffin—or adrenal—sympathetic system. For the loss of flesh and strength, and the impairment of general vigor is out of all proportion to the supposed local cause. Furthermore, the benefit to be obtained by feeding some derivative of the whole adrenal gland, especially the adrenal nucleoproteins (and not epinephrin) is very suggestive.

To sum up the foregoing observations, it is reasonable to believe that the etiology of hyperfunctionation of the stomach, with or without ulcer, is not a "neurosis" or pathologic condition of the vagus, but a defect or failure in functionation in the gastric and possibly other parts of the sympathetic system, including the adrenal gland; that the ulcer is a secondary and incidental lesion; that the primary cause of the whole disturbance is a fatigue which interferes with the functionation of the sympathetic terminals, especially of the gastric sympathetic; that the symptoms are to be interpreted according to the functions of the involuntary nerves; and that the treatment, whether medical or mechanical, to be successful should constantly have these other abnormalities in view rather than the apparently secondary ulcer.

The acute gastric hypofunctionation is so constant and manifest an accompaniment of all extremes of fatigue that it is evidently traceable, like the condition in the voluntary muscles, to defective functionation in all the gastric nerve terminals. Presumably, when it becomes chronic, the activating or vagus terminals continue their defective functionation, and the result is a corresponding decrease in the gastric motility and secretion. The usual treatment is, of course, designed to stimulate and supplement these deficiencies, and because of its experimental specific activity, feeding with some thyroid preparation, especially an alcoholic extract, is usually of great benefit. At the same time, in connection with the apparent failure of the gastric vagus, it should be noted that the symptoms of hypofunctionation of the stomach and intestinal tract are also a part of the symptoms commonly accepted as those of hypothyroidism.

As asserted before, the functional disorders of the thyroid gland, like those of the stomach, are apparently of the same character and occur in the same type of "nervous" subjects. The exacerbations and remissions of these disturbances also occur under the same conditions

of fatigue, and the symptoms and pathologic physiology in both organs are mostly traceable to abnormal functioning by the involuntary nerves.

The function of the thyroid is generally conceded to be connected with oxidation, and the acceleration of metabolism throughout the body. The gland possesses this power through its product, which apparently activates the terminal filaments of the autonomic or "driving" portion of all of the involuntary nerves. For an alcohol extract or one in which there has been more or less hydrolysis, such as can be made by boiling (and filtering), a slightly alkaline saline extract, gives quite definite and immediate reactions.⁴

An extract made with distilled water, by the way, is inert. Thus a hydrolyzed or alcohol extract of the thyroid when injected into dogs appears to be vasodilator; a stimulant for the contractions of voluntary and involuntary muscles apparently through the terminals of their "activating" nerve supply; a stimulant in the same way for the stomach and pancreas (through the vagus) and also probably the salivary glands. But no material from either the normal or pathologic hyperthyroid gland will produce any appreciable degree of tachycardia. That is, so far as has been determined, extracts of the thyroid show no effect on the sympathetic or general inhibitory and vasoconstricting system, but do show a vigorous stimulating influence on the functions believed to be performed by the opposing group of nerve terminals, especially the vagus. The thyroid apparently "activates" the autonomic and not, as is generally believed, the sympathetic system. This corresponds with the majority of the typical symptoms which are accepted as indicating the existence of overactivity of the gland or hyperthyroidism. The flushed and moist or sweaty skin; the excess of the oral and salivary secretions; the pounding, and overacting (vagus) rather than the merely rapid (cardio-accelerator) heart; the good or excessive appetite (vagus hunger contractions); the frequent or loose bowel movements, are all signs, not of sympathetic but of autonomic or vagus activity.

The exophthalmos, which is not constant and may exist without any other evidence of hyperthyroidism, is generally believed to be due to irritation or stimulation of the sympathetic, but the mechanism by which it is brought about is unknown. The tachycardia, which is constant in hyperthyroidism, is traceable directly to the cardio-accelerator or a sympathetic nerve. But it cannot be produced experimentally within the usual laboratory period of two or three hours, although it can be brought about by feeding thyroid long enough to produce the usual acceleration of metabolism. Therefore, it seems

4. *Am. J. Physiol.* 48:79 (Feb.) 1919.

probable that the simple rapid pulse which is so characteristic of hyperthyroidism is not due to the effect of the thyroid product on the cardio-accelerator nerve, but to the general metabolic activity. The overacting heart which is accompanied by a sensation of thumping or pounding, however, is probably dependent on the direct stimulation of the cardiac vagus by the thyroid secretion.

In contrast to the signs of autonomic stimulation which indicate hyperthyroidism, the opposite extreme of functioning, or hypothyroidism, is shown chiefly by a deficiency of autonomic activity. This closely simulates ordinary fatigue, and can only be differentiated from it by the presence of at least a perceptible thyroid enlargement and by the effects of thyroid feeding. Unfortunately the latter, because of the different action of different thyroid products, is uncertain.

To recapitulate then: the thyroid through its secretion apparently activates, not the inhibitory or sympathetic system, but all of the functions which are dependent on the impulses discharged through the vagus or autonomic terminals. As the vagus supplies the thyroid, the gland should, therefore, be "auto-activated." That is, the secretion returns to its source and gains access to the thyroid epithelium through its laryngeal, and so vagus, or presumably "activating" nerve supply. It is important to recognize this probability because of its bearing on the mode of action of thyroid feeding and of organ therapy in general. Certainly there are many cases of myxedema which cannot be cured in the usual way, or are made worse by thyroid feeding, and ultimately die from hypothyroidism. Cretinism, or congenital myxedema, is similarly disappointing, and even more "resistant" to thyroid feeding. It is also well known that complete extirpation of the thyroid (in man) is fatal.⁵ These facts indicate that the patient who is benefited by thyroid feeding must possess a certain minimum amount of thyroid epithelium and it must be capable of more or less normal functioning. Otherwise the ingested thyroid material is inert or harmful. Evidently after passing through the digestive tract and the liver, this material emerges into the circulation, probably as an iodized amino-acid which, though it retains some affinity for the vagus terminals and experimentally may activate them, nevertheless, does not perform the full function of the normal thyroid product. That is, the ingested material, to be efficient, must first pass through the patient's own thyroid epithelium. If this epithelium or its vagus nerve supply, or

5. Some surgeons apparently believe that the entire thyroid gland can be removed with benefit to the patient in cases of hyperthyroidism. If later there did not follow the fatal cachexia thyreopriva which was proved by Kocher to be the result of this operation; then either the surgeon did not remove the entire gland or there must have existed some "aberrant" thyroid tissue.

both, fail to functionate, thyroid feeding is useless. There is some evidence which suggests that the nearer the medicament approaches in chemical structure that of the normal thyroid epithelium, the better is the effect; but even then, if the gland or its nerve supply is absent or inefficient, the feeding of any known thyroid product will not succeed. Probably all kinds of organ therapy are subject to the same general laws and, therefore, ovarian feeding, for example, after total oöphorectomy should be useless or nearly so.

The histologic changes in the thyroid alveoli which are characteristic of hyperthyroidism may occur diffusely and throughout the gland or be more or less localized circumferentially around an encapsulated cyst or adenoma. Under the latter conditions, it should be noted that the diseased tissue from which the superabundant secretion is supposed to proceed can practically all be excised by enucleation of the tumor, and the result is generally a complete relief from the hyperthyroid symptoms.

Any simple, or quiescent, goiter may, after the patient has been subjected to conditions which induce fatigue, be accompanied by signs of hypothyroidism or hyperthyroidism. Moreover, the same individual may at different times show signs which indicate opposite extremes of thyroid activity. That is, the functional thyroid diseases are interchangeable. Under conditions which insure rest, a moderate hyperthyroidism becomes regularly a hypothyroidism, but under fatigue, exophthalmos is usually added to the symptoms of hyperthyroidism. All of these disturbances, however, begin with a simple hypertrophy of the gland, which seems to be an enlargement to compensate for excessive demands on a possibly weak organ. The cysts, or adenomas, which form after the simple hypertrophy, are apparently incidents of the congestion, and may be reactions to a primary hemorrhage during this congestion for the promotion of glandular activity.

The functional thyroid diseases seem, then, to begin with a simple hypertrophy, which is accompanied by more or less marked evidences of hypothyroidism. These, it should be repeated, differ from the signs of fatigue only by the presence of the "goiter." From this primary stage of hypothyroidism the symptoms may advance into myxedema or into those of hyperthyroidism, and then finally into exophthalmic goiter. If recovery occurs, the symptoms "regularly" recede through these different stages, although the exophthalmos is generally the last abnormality to disappear. In many cases the development of hyperthyroidism occurs quite suddenly, but the number of those which follow the "regular" course is sufficient to indicate the probable origin of the disturbance. This is most reasonably explained by fatigue, or a condition which affects primarily the functions performed by the terminal filaments of all nerves, including those of the involuntary system.

The latter presumably control the functional activity of the thyroid as they do that of the stomach. If they did not so control it, any excess of thyroid product would immediately start and perpetuate a hyperthyroidism. For this gland, like the stomach, seems to be "auto-activated" through its vagus nerve supply. The restraining, or inhibitory, influences are probably dependent, as in the stomach, on the sympathetic or chromaffin system, which includes the adrenal gland (and possibly also the pituitary). It is worth noting, by the way, that the adrenals are believed, like the thyroid and stomach, to be supplied by filaments from both the vagus and the sympathetic. Therefore, if the thyroid-autonomic group activates, and the chromaffin system or the adrenal-sympathetic group inhibits, each viscus, then any overactivity of the thyroid should be met by stimulation of the adrenals and inhibition of the thyroid through its sympathetic nerve supply. If fatigue interferes with the functionation of the thyroid sympathetic filaments, as it seems to in the stomach, hyperthyroidism is inevitable.

The differential diagnosis between hypothyroidism and hyperthyroidism, because of the many mixed types of these disorders, is often clinically impossible. The most conclusive test of hyperthyroidism is furnished by the calorimeter, but it is not readily to be obtained. The histologic examination of an excised portion of the gland is definite when it includes the disease. Clinically, and in general, therefore, one must compare the signs which indicate autonomic or vagus activity with those which show their absence, or only the presence of impulses from the inhibiting sympathetic. If the evidences of autonomic activity preponderate in the form of more or less vigorous functionation in several organs as against the quiescence or inactivity of others, then the thyroid is probably overacting. If there is a general inactivity of the viscera, the condition is one of hypothyroidism. As mentioned previously, exophthalmos is by no means always a proof of hyperthyroidism; nor is a simple tachycardia which seems to be only a part of the general increased metabolism. A rapid pulse, by the way, is the regular accompaniment of extreme asthenia from any cause, and "weakness" is one of the most constant accompaniments of all thyroid abnormalities.

Some aid in the diagnosis can be obtained from a study of the history and the probable stage presented in the course of the disease. This is generally suggestive of some initial failure or deficiency, and, therefore, of a treatment which should conserve and "help out" the thyroid rather than destroy this evidently important gland. Hence, when the symptoms are not manifestly those of overactivity of the functions which are stimulated by the autonomic or vagus system, a cautious trial of "feeding" one or another thyroid derivative is rea-

sonable. Benefit, and even ultimate cure, can often be obtained in some cases of supposed hyperthyroidism by the administration, frequently repeated, of a few minims of an alcohol or a hydrolyzed extract of the thyroid; or $\frac{1}{100}$ or $\frac{1}{50}$ of a grain of the dried nucleoprotein obtainable by precipitation with 10 per cent. acetic acid from a saline extract of the hashed fresh gland; from $\frac{1}{20}$ to $\frac{1}{4}$ grain doses every three or four hours of the commercial desiccated thyroid powder is less often satisfactory. It is also reasonable, in cases of manifest hyperthyroidism, to attempt to reinforce the presumably weak or defective inhibitory or sympathetic-adrenal system by feeding some derivative of the adrenal gland. Epinephrin is clinically not as beneficial as an alcohol or a hydrolyzed extract of the whole gland, or as the adrenal nucleoprotein material (made like the corresponding thyroid nucleoproteins).

Surgery, however, has been abundantly proved to be the surest and safest treatment for all definitely hyperthyroid conditions. When the anatomic lesions which are characteristic of the disease can be localized with reasonable certainty in some particular portion or portions of the organ, their excision is curative. This localization can be determined with more or less accuracy because the hyperplastic alveoli lie, for the most part, closely around or in circumscribed tumors, and their enucleation or excision destroys or removes the source of the excessive secretion. Similarly, when the disease is probably confined to one lobe, as indicated by its greater size and density and vascularity, the removal of that lobe is generally indicated. Unfortunately, the lesion is most commonly scattered diffusely throughout the whole organ, as shown by its symmetrical hypertrophy and even consistency. Under these conditions, hemithyroidectomy is more apt partially or completely to fail than to succeed. The operation is designed to cut down the apparent excessive amount of thyroid secretion, and so check or stop the presumable "auto-activation." But the hyperplastic and hyperactive alveoli, even if they remain in much less than half the original gland, may continue the disturbance. I have seen at least one death with intensification of all the hyperthyroid symptoms after a practically complete thyroidectomy. Therefore, in view of these uncertainties, which apparently involve an extensive or general failure of the inhibitory apparatus as well as a theoretical local failure of thyroid inhibition, I advise the ligation, in two stages under local anesthesia, of all four of the chief thyroid vessels. The lower two can be easily reached behind the great vessels by an incision along the lower end of the posterior border of the sternomastoid, and should be tied first because there is practically none of the post-operative pain and consequent reaction which follows a wound nearer the pharynx. The object of the ligation operation is to cut off as

tion in an infected dog with induced uranium nephritis. We have at the same time had occasion to follow the uninterrupted course of the disease and have observed the various symptoms described by Krumbhaar. Emaciation and weakness occurred regularly. Stiffness of the legs, falling of the hair, keratitis, anorexia, vomiting and diarrhea were present in varying degrees, but the edema observed by some investigators, we did not see.

METHODS

Only dogs were used. They were placed on a constant diet of beef heart and cracker dust with sodium chlorid, 1 gm., every twenty-four hours. A number of preliminary determinations were made without the addition of the sodium chlorid to the diet. The plasma chlorids were determined by the method of McLean and Van Slyke.⁴ The blood for this purpose was drawn from the jugular vein from twenty to twenty-four hours after the last feeding. The blood was collected under liquid petrolatum in centrifuge tubes containing crystals of potassium oxalate, immediately centrifuged and the plasma pipetted off. The urine for chlorid determinations was that obtained by catheterization from twenty to twenty-four hours after the last feeding and one hour after giving 100 c.c. of water by stomach tube. Determinations were made by the McLean and Van Slyke method as applied to urine.⁴ These determinations were then indicated in the table as grams of chlorid per liter of urine. The amount of urine obtained by catheterization was added to the amount of urine collected in the bottle under the metabolism cage and was taken as representing the total volume of urine in twenty-four hours. The amount of chlorids for twenty-four hours was calculated on the basis of concentration represented in the catheterized specimens, though this did not allow for the varying concentration during the twenty-four hours. All chlorid determinations were made in duplicate.

After the dogs had been studied in a state of health, they were infected with trypanosomes by injecting into the jugular vein the citrated blood of a medium-sized rat, heavily infected with *T. equiperdum*. The blood was obtained from the rats by severing the vessels of the neck under anesthesia and allowing the blood to flow into warm sodium citrate solution (2 per cent. in distilled water).

The blood of the dogs was examined for the presence of trypanosomes in from about seven to ten days. Following their appearance and multiplication, anemia rapidly developed and became quite marked in the course of several weeks, or at times sooner, according to the severity of the infection. After the anemia had been definitely established, observations were again conducted on plasma and urinary chlorids and on renal function.

RESULTS

The results of determinations in normal dogs alone are given in Tables 1 and 2. These normal figures correspond to the findings of Austin and Jonas,⁵ in the fact that the plasma chlorids are relatively high as compared to man, the urinary chlorids low. In Tables 3 and 4 are recorded the figures obtained with two dogs, first in a state of

4. McLean, F. C., and Van Slyke, D. D.: A Method for the Determination of Chlorids in Small Amounts of Body Fluids, *J. Biol. Chem.* **21**:361, 1915.

5. Austin, J. H., and Jonas, L.: Effects of Diet on the Plasma Chlorids and Chlorid Excretion in the Dog, *J. Biol. Chem.* **33**:91, 1918.

health and then after infection with *T. equiperdum*. In one of these a uræmium nephritis was later produced in order to determine the effect of nephritis in the presence of anemia on the chlorids of the plasma and urine.

TABLE 1.—NORMAL PLASMA AND URINARY CHLORIDS

Dog 1.—Female; weight, 11,200 gm.; constant diet, minced beef heart, 300 gm., cracker dust, 50 gm.; in twenty-four hours.

Day of Experiment	Plasma Chlorids, Gm. per Liter	Urine					Phenol-sulphone-phthalein, per Cent.		Blood	
		Amount per 24 Hours, C.c.	Chlor-ids per Liter, Gm.	Chlorids in 24 Hours (calcu-lated), Gm.	Albu-min	Casts	1st Hour	2d Hour	Red Blood Cells	Hb., per Cent.
1	6.12	350	1.0	0.35	0	0
4	6.12	220	0.8	0.17
6	6.0	250	1.5	0.37
8	6.12	221	0.4	0.08
10	6.25	235	0.6	0.14	0	0	50	10	5,460,000	92

TABLE 2.—NORMAL PLASMA AND URINARY CHLORIDS

Dog 2.—Female; weight, 11,000 gm.; diet, same as Dog 1.

Day of Experiment	Plasma Chlorids, Gm. per Liter	Urine					Phenol-sulphone-phthalein, per Cent.		Blood	
		Amount per 24 Hours, C.c.	Chlor-ids per Liter, Gm.	Chlorids in 24 Hours (calcu-lated), Gm.	Albu-min	Casts	1st Hour	2d Hour	Red Blood Cells	Hb., per Cent.
1	5.87	460	6.0	2.76	0	0
4	5.60	255	4.1	1.04
6	6.00	364	2.4	0.87
9	5.87	378	3.4	1.28
11	5.87	410	2.8	1.14	0	0	60	5	5,820,000	98

TABLE 3.—PLASMA AND URINARY CHLORIDS IN HEALTH AND IN STAGE OF ANEMIA FROM *T. EQUIPERDUM* INFECTION

Dog 4.—Female; weight, 9,950 gm.; diet, beef heart, 250 gm.; cracker dust, 75 gm.; sodium chlorid, 1 gm. in twenty-four hours.

Day of Experiment	Plasma Chlorids, Gm. per Liter	Urine					Phenol-sulphone-phthalein, per Cent.		Blood	
		Amount per 24 Hours, C.c.	Chlor-ids per Liter, Gm.	Chlorids in 24 Hours (calcu-lated), Gm.	Albu-min	Casts	1st Hour	2d Hour	Red Blood Cells	Hb., per Cent.
1	6.125	365	2.5	0.91	0	0
3	6.0	420	2.2	0.92
6	6.0	410	1.8	0.73
8	6.125	540	2.1	1.10	0	0	65	10	7,250,000	110
Period of Anæmia										
37	6.50	620	3.1	1.90	0	0	3,050,000	40
39	6.50	710	3.3	2.30	0	0
41	6.62	640	4.0	2.56	0	0	55	10

TABLE 4.—PLASMA AND URINARY CHLORIDS IN HEALTH, IN STAGE OF ANEMIA FROM *T. EQUIPERDUM* INFECTION AND IN URANIUM NEPHRITIS

Dog 6.—Female; weight, 10,400 gm.; diet, same as Dog 4

Day of Experiment	Plasma Chlorids, Gm. per Liter	Urine					Phenol-sulphone-phthalein, per Cent.		Blood	
		Amount per 24 Hours, C.c.	Chlorids per Liter, Gm.	Chlorids in 24 Hours (calculated), Gm.	Albumin	Casts	1st Hour	2d Hour	Red Blood Cells.	Hb., per Cent.
1	6.25
2	6.12	207	6.0	1.20	0	0
5	6.37	520	2.1	1.09
6	331	3.2	1.05	50	15
7	510	3.8	1.90	0	0	6,050,000	98
Period of Anemia										
25	6.75	430	5.1	2.11	0	0	2,850,000	50
27	6.87	451	3.3	1.41
29	7.12	420	4.1	1.70	0	0	55	5
Period of Nephritis. Uranium nitrate, 0.02 gm., subcutaneously, given 31st day										
34	430	1.1	0.47	Heavy cloud	Many gran.
36	8.12	544	1.0	0.54

The tables indicate that there was a constant and fairly marked increase in the plasma chlorids during the period of active infection and anemia. This is apparently not due to an impairment of chlorid excretion, as can be seen by the ample excretion of chlorids in the urine. It would appear desirable to have observations on the plasma chlorids in the anemias of man to throw further light on this question. Renal function as measured by phenolsulphonephthalein excretion shows practically no difference between the stage of infection and that of health. Neither albumin nor casts were found in the urine of the infected dogs. The single observation in Dog 6 on the effect of nephritis presents findings that could be expected as a result of the added factor of hindered excretion. Such impaired excretion is demonstrated in this case.

CONCLUSIONS

1. The chlorid concentration in the plasma is raised in the dog during the active stage of infection with *T. equiperdum* at the period when anemia is a prominent feature.

2. This increased concentration of chlorids in the plasma is not dependent on retention due to impaired capacity of the kidneys to excrete chlorids.

3. In one observation, uranium nephritis in a dog rendered anemic by *T. equiperdum* was followed by a still higher concentration of chlorids in the plasma associated with a definite impairment in the renal capacity for excreting chlorids.

THE CLINICAL SIGNIFICANCE OF SLIGHT NOTCHING OF THE R-WAVE OF THE ELECTRO- CARDIOGRAM *

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As a result of extensive electrocardiographic studies in past years, the questions of the more common disturbances of the cardiac mechanism have for the time being been settled, and numerous investigators have directed efforts to the elicitation of electrocardiographic evidences of myocardial involvement. Carter¹ has summarized the knowledge of the aberrant beat and the electrocardiogram associated with a lesion of either branch of the atrioventricular bundle. The ventricular complex is said to be characterized by a notched or bizzare R-wave of high amplitude, a QRS interval exceeding 0.10 second and an exaggerated T-wave usually opposite to the initial deflection. Such curves are indicative of an extensive pathologic process and imply a grave prognosis. Oppenheimer and Rothschild² have described intra-ventricular or arborization block. The underlying pathology of their cases was coronary sclerosis or disseminated patchy sclerosis of the myocardium predominate in the Purkinje network. The electrical curves are of low voltage, the R-waves notched and the QRS interval exceeds 0.10 second. Robinson³ has reported cases with abnormal ventricular complexes consisting of widened and notched QRS groups which he regarded as resulting from functional impairment of intra-ventricular conduction. Recently Neuhof⁴ has set an arbitrary standard of 0.07 second for the upper limit of base line width of a normal R complex and presented cases with grave myocardial disease in which the R-waves measured from 0.07 to 0.12 second. He believes that such prolongation of R indicates myocarditis. (The width of the normal R-wave has been assigned different values by various authors: Lewis,⁵ 0.03 to 0.04 second; Einthoven,⁶ 0.03 second; Kraus and Nicolai,⁶ 0.06 second; Oppenheimer and Rothschild give 0.10 second for the upper limit of normal.)

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1. Carter: Arch. Int. Med. **13**:803, 1914; idem. **22**:331, 1918.

2. Oppenheimer and Rothschild: J. A. M. A. **69**:429, 1917.

3. Robinson: Arch. Int. Med. **18**:830, 1916.

4. Neuhof: Arch. Int. Med. **22**:45, 1918.

5. Lewis: Heart **4**:242, 1913.

6. Quoted by Kahn: Ergebn. d. Physiol., 1914, p. 93.

DATA OF AUTHOR'S CASES

Case No.	Clinical Diagnosis	Rhythm	Type of Electrocardiogram	Leads Affected	R Complex	P-R Interval	Remarks
1	Syphilitic myocarditis; nephritis	Atrial fibrillation	Left Vent.	L III	R III 0.06	—	Death
2	Myocarditis; aortitis; emphysema	Atrial fibrillation	Normal	L III L II	R I 0.08 II 0.07	—	Death
3	Syphilitic myocarditis; nephritis	Normal	Right Vent.	L I (sl.) L III	III 0.08 R III 0.065	0.22	Death
4	Rheumatic myocarditis; mitral disease	Atrial fibrillation	Left Vent.	L III	R I 0.06 II 0.08 III 0.08	—	Death
5	Rheumatic myocarditis	Atrial fibrillation	Normal	L I L III	R I 0.07 II 0.08 III 0.05	—	
6	Rheumatic myocarditis; nephritis	Normal	Left Vent.	L III	R I 0.06 II 0.06 III 0.03	0.165	Recurrent tonsillitis and arthritis
7	Myocarditis; arterio-sclerosis	Premature beats	Left Vent.	L III	R I 0.04 II 0.06 III 0.07	I 0.16 II 0.16 III 0.20	Subject to anginal attacks
8	Nephritis; myocarditis; syphilis	Normal	Left Vent.	L III	R I 0.06 II 0.06 III 0.06	I 0.16 II 0.18 III 0.18	Later admitted with atrial flutter; death
9	Syphilitic myocarditis; nephritis	Normal	Left Vent.	L III L II	R I 0.07 II 0.07 III 0.06	I 0.14 II 0.15 III 0.16	
10	Rheumatic myocarditis; mitral disease	Normal	Normal	L I L II L III	R I 0.06 II 0.06 III 0.05	I 0.12 II 0.14 III 0.16	
11	Syphilitic myocarditis; aortitis	Normal	Left Vent.	L III	R I 0.07 II 0.07 III 0.07	I 0.14 II 0.16 III 0.16	Death later from bronchopneumonia
12	Rheumatic myocarditis; pericarditis; mitral disease	Premature beats	Normal	L III	R I 0.05 II 0.08 III 0.08	I 0.17 II 0.18 III 0.18	Atrial premature beats constant; inverted P in L III
13	Syphilitic aortitis; aneurism; myocarditis	Normal	Left Vent.	L III	R I 0.07 II 0.08 III 0.08	I 0.14 II 0.16 III 0.16	Chancre 3 years ago
14	Myocarditis; arterio-sclerosis	Normal	Left Vent.	L III	R I 0.06 R II 0.06 III 0.07	I 0.18 II 0.22 III 0.18	No cardiac symptoms
15	Rheumatic myocarditis; mitral disease	Normal	Normal	L III L II	R I 0.07 II 0.07 III 0.07	I 0.22 II 0.22 III 0.22	Acute appendicitis; no cardiac symptoms
16	Myocarditis; arterio-sclerosis	Atrial fibrillation	Left Vent.	L I L III	R I 0.06 II 0.05 III 0.06	—	
17	Chronic myocarditis	Atrial fibrillation	Left Vent.	L I L III	R I 0.08 II 0.07 III 0.08	—	
18	Myocarditis; arterio-sclerosis	Atrial fibrillation	Left Vent.	L I L II	R I 0.07 II 0.07 III 0.04	—	Chronic alcoholism
19	Chronic valvular disease; mitral; aortic; pericarditis	Normal	Normal	L I L III	R I 0.06 II 0.08 III 0.08	Average 0.20	Etiology, rheumatic fever
20	Cardio-sclerosis	Normal	Left Vent.	L III	R I 0.06 II 0.06 III 0.06	Average 0.20	
21	Chronic valvular disease, mitral	Normal	Right Vent.	L I L II	R I 0.07 II 0.07 III 0.05	Average 0.17	No cardiac symptoms; etiology not known
22	Syphilis	Normal	Left Vent.	L III	R III 0.04	I 0.12 II 0.16 III 0.10	
23	Syphilis	Normal	Left Vent.	L III	R I 0.07 II 0.08 III 0.07	Average 0.14	
24	None made	Normal	Left Vent.	L III	R I 0.06 II 0.07 III 0.06	I 0.11 II 0.12 III 0.10	Attacks of tachycardia

DATA OF AUTHOR'S CASES—(Continued)

Case No.	Clinical Diagnosis	Rhythm	Type of Electrocardiogram	Leads Affected	R Complex	P-R Interval	Remarks
25	Chronic nephritis	Normal	Normal	L III	R I 0.04 II 0.06 III 0.06	III 0.16	
26	None made	Normal	Normal	L III L II	R I 0.03 II 0.05 III 0.05	Average 0.14	Attacks of premature beats and precordial pain
27	None made	Normal	Left Vent.	L III L II	R I 0.05 II 0.05 III 0.05	I 0.14 II 0.16 III 0.16	Palpitation; B. P., 149-119
28	Syphilis	Normal	Normal	L III	R I 0.06 II 0.07 III 0.07	I 0.16 II 0.15 III 0.16	
29	Not made	Normal	Left	L III	R I 0.04 II 0.07 III 0.08	I 0.14 II 0.17 III 0.17	Palpitation; systolic pressure 180 at times
30	Not made	Normal, except for premature beats	Normal	L I	R I 0.06 II 0.07 III 0.07	I 0.12 II 0.14 III 0.14	Slight precordial pain at times; premature beats, atrial constantly present

An examination of the literature of the past eight years with reference to that point reveals ample evidence, based on experimental, pathologic and clinical studies, for regarding variations in the QRS group as due to structural or functional changes in the main bundle, the principal branches or the ramifications of the Purkinje network.

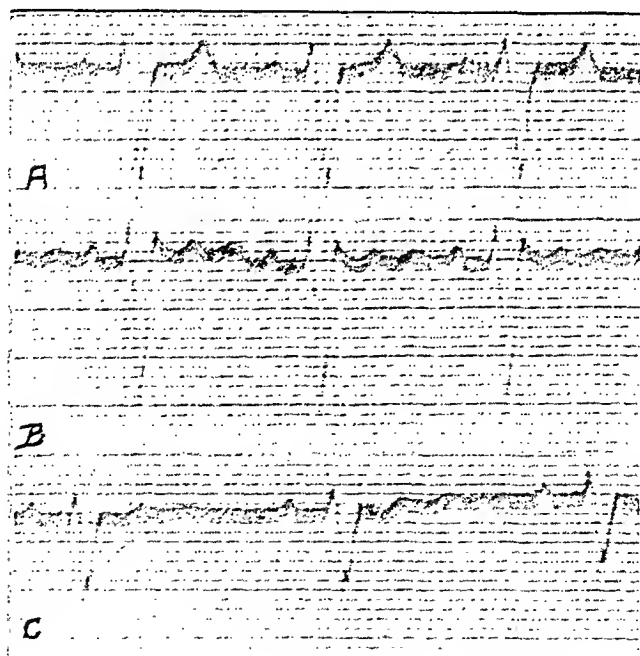


Fig. 1.—A, on admission; B, after 30 c.c. of digitalis; C, after 80 c.c.

The purpose of this paper is to call attention to slight notching or localized thickening of the R-wave, and by correlation of this with other abnormalities of the electrocardiogram when they are present, and with the clinical findings, to endeavor to establish a basis for its

significance, and to postulate its possible value as an evidence of myocardial involvement when that is the principal deviation from the normal that is found in the electrocardiogram and when physical examination affords no positive evidence of invasion of the myocardium.

The accompanying table comprises in a general way three groups of cases: those with severe myocardial disease, readily recognizable clinically, in many of which atrial fibrillation was present; a second group, less severe clinically, but including cases in which a diagnosis of myocarditis was justifiable; and a smaller number in which the history or certain physical signs suggested the possibility of myocardial disease, although there had never been any failure of cardiac

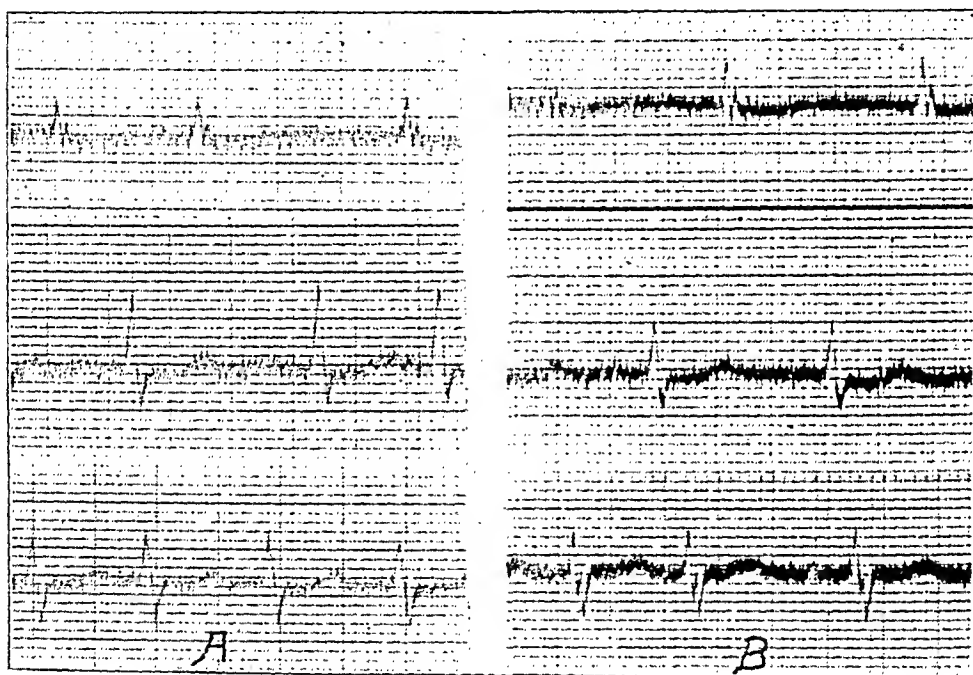


Fig. 2.—Case 4. A, Jan. 20, 1916; B, Oct. 14, 1917.

reserve, or, in a few cases, any symptoms referable to the heart. The cases of known etiology in which this notching has been observed have rheumatic infection, syphilis or arteriosclerosis as the causative factors of the cardiac disease.

The discussion is limited to R complexes of base line width of less than 0.10 second. In the majority of cases cited the notching occurred only in the third lead, or was usually more marked in that lead when present in others. In about one-half of the cases the electrocardiogram was of the type associated with left ventricular preponderance. These facts make the presence of such notching of special value in judging the left heart. In many cases there was no

appreciable prolongation of the P-R interval; occasionally it was prolonged only in one lead, the third, or less frequently the second, usually in association with the greatest degree of notching.

The notching has been observed in a few cases to increase in degree. This is believed to indicate an extension of the pathologic process

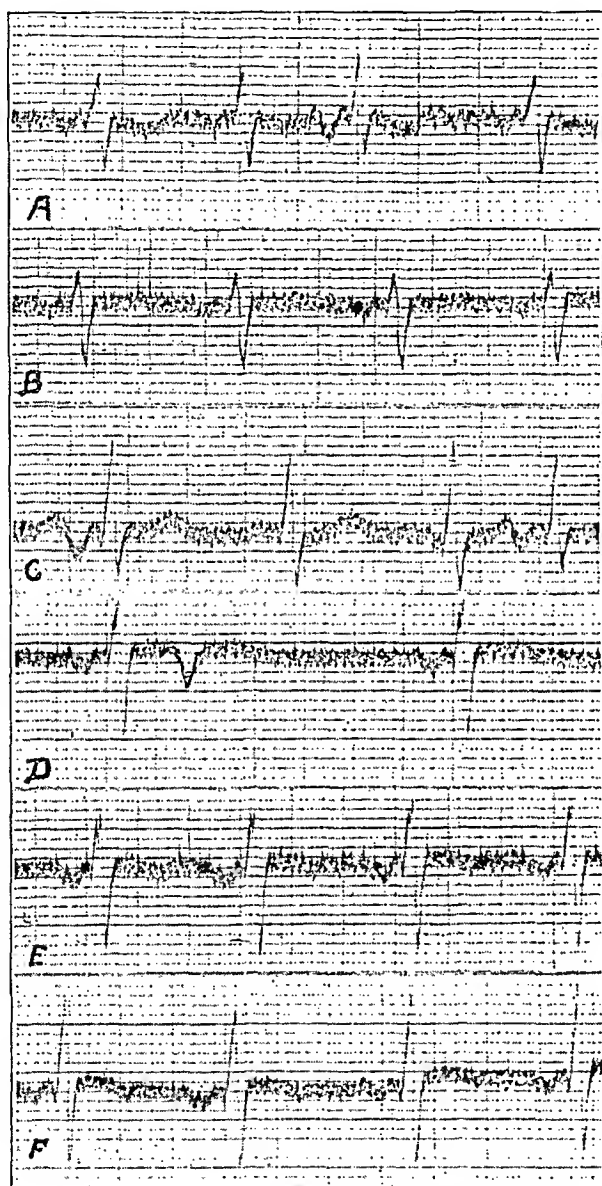


Fig. 3.—Case 12. Lead III. A, June 6, 1917; B, June 16, 1917; C, Oct. 24, 1917; D, March 28, 1918; E, April 25, 1918; F, June 2, 1918.

(Case 4). On the other hand, the notching may be transient or decrease under conditions that favor functional improvement in the conducting system (Case 12). Changes may be produced by digitalis; Figure 1 is interpreted as showing, first, improvement, and later, depression of the conducting system by that drug. That the notching may decrease or disappear in cases of syphilis following treatment is

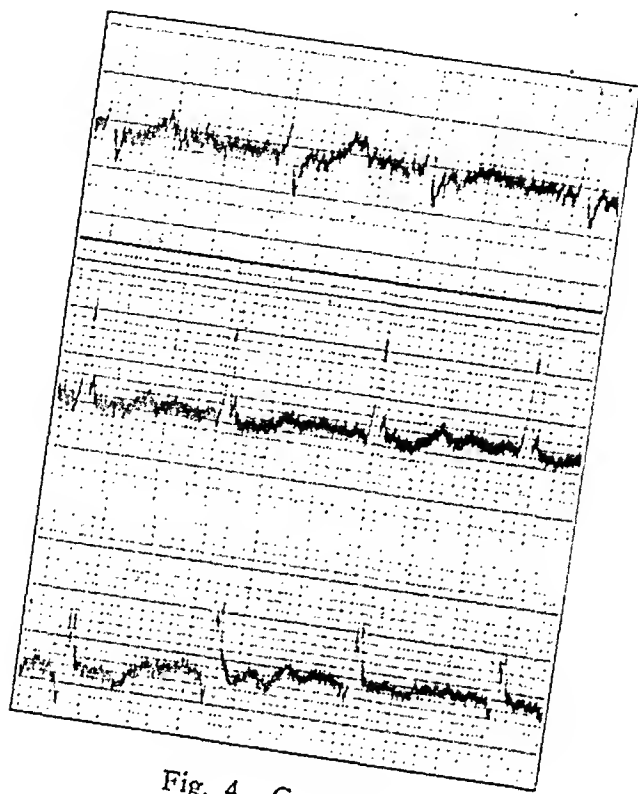


Fig. 4.—Case 2.

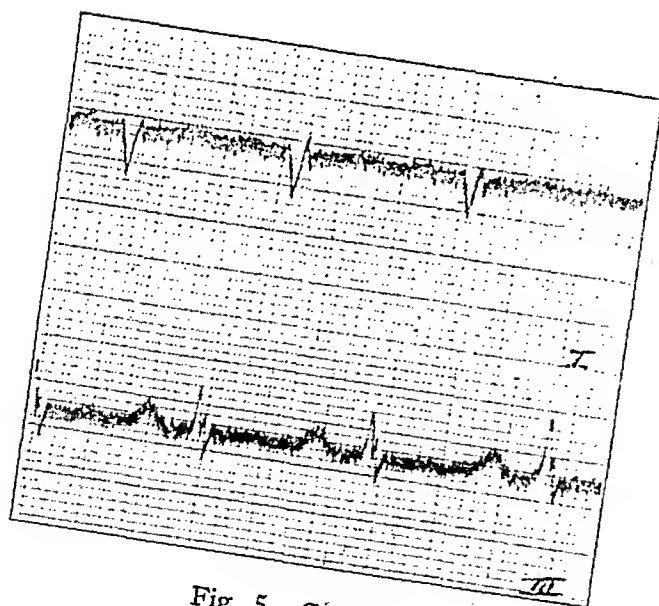


Fig. 5.—Case 3.

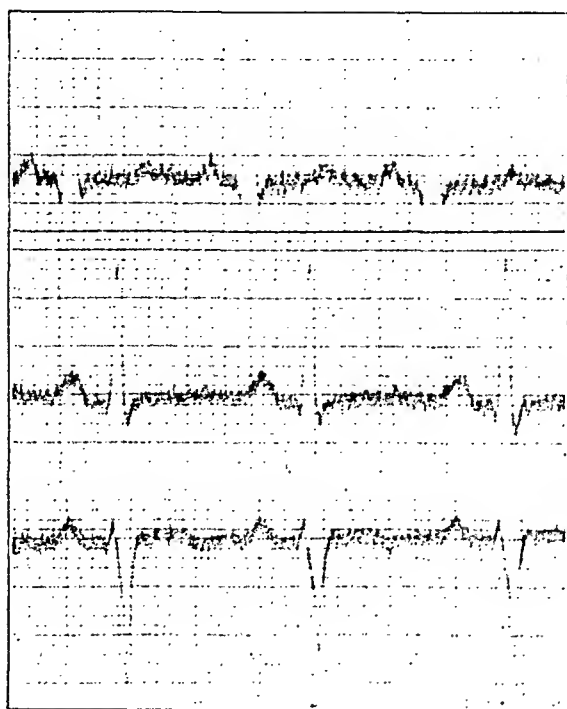


Fig. 6.—Case 6.

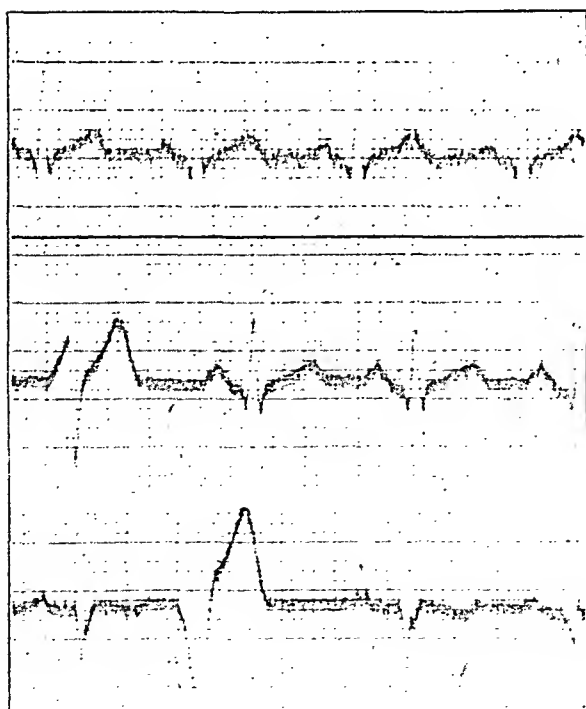


Fig. 7.—Case 7.

conceivable, although it has not been observed in any of the cases studied.

There was no quantitative relation between the notching and the clinical signs or symptoms, and it was not always present in what appeared otherwise to be similar conditions. It is not of definite value in prognosis, but it is believed, however, when constantly present in any given case, to indicate slight architectural changes, fibrotic in nature, in the finer ramifications of the intraventricular conducting system.

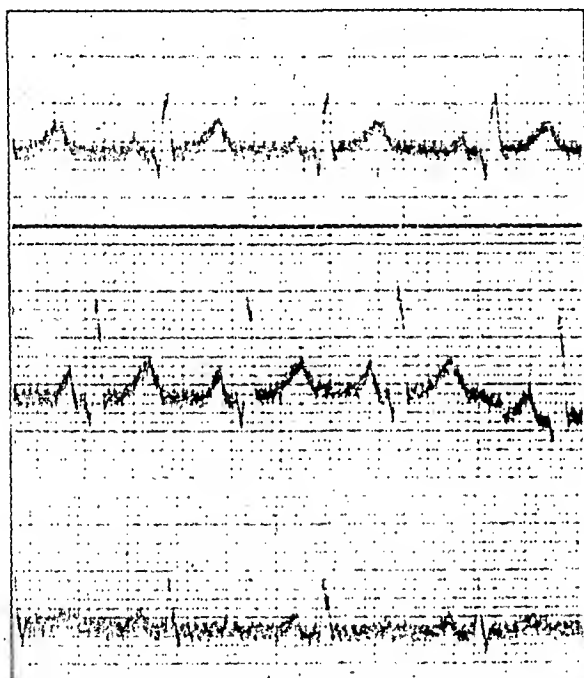


Fig. 8.—Case 10.

SUMMARY

Slight notching or localized thickening of the R complex of the electrocardiogram is frequently encountered in cases of unquestionable myocarditis. It often occurs in the third lead only, and in the majority of cases is associated with left ventricular preponderance. It may be present in an otherwise normal electrocardiogram, and is seen in cases in which physical examination affords but little evidence of myocardial disease. While no quantitative value can be assigned to such notching, it is believed, when permanent, to indicate pathologic changes in the myocardium, and when transient to reveal a temporary or potential defect in the conducting system, and is thus of aid in differentiating purely valvular lesions or functional affections of the heart. Illustrative cases are cited.

REPORT OF CASES

CASE 4 (Fig. 2).—Mrs. W. F., aged 57 years. This patient was admitted to the hospital four times during the previous two years, each time presenting marked cardiac decompensation. There was a history of repeated attacks of rheumatic fever. The clinical diagnosis was myocarditis, chronic valvular disease, mitral stenosis and insufficiency, and atrial fibrillation. Compare "A" and "B," Figure 2.

CASE 12 (Fig. 3).—T. L., a boy of 16 years. When first admitted, June 4, 1917, he complained of pain in the chest, weakness and fever. This illness was preceded by sore throat. He said that he had been unwell during the previous year and also that four years previously he had been in a hospital in Austria, but did not recall anything about the trouble at that time. The clinical diagnosis made was: chronic mitral endocarditis and chronic peri-

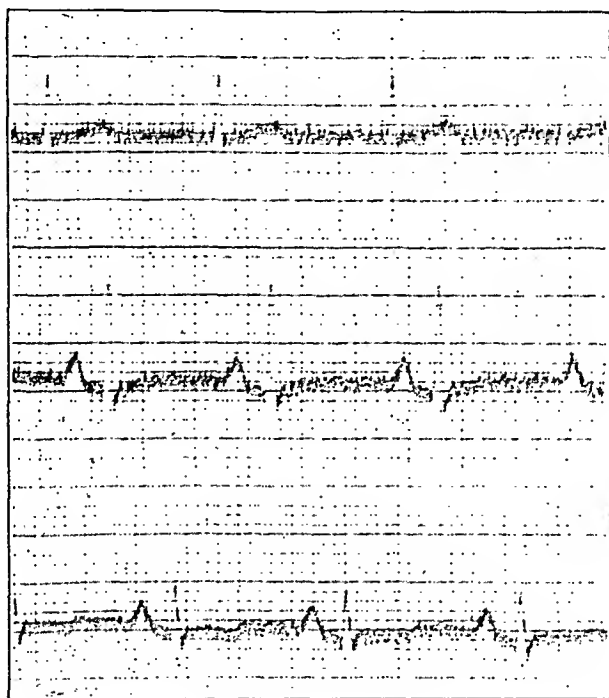


Fig. 9.—Case 25.

carditis, rheumatic in origin. The cardiac rhythm was disturbed by many premature beats arising in the atrium. (See "A" and "B," Fig. 3.)

The second admission was in August, 1917, because of pain in the heart. He improved and left the hospital after fifteen days.

Sept. 20, 1917, he again entered the hospital, this time suffering from acute rheumatic fever involving the right knee, shoulder and ankle joints. Records taken at this time showed short paroxysms of tachycardia. Slight notching of R in the second and third leads is seen (Fig. 3, "C").

March 28, 1918, he returned to the hospital with acute bronchitis. The notching was more marked at this time (Fig. 3, "D" and "E").

A record taken two months later, after he had left the hospital, showed the notching much diminished, although still present (Fig. 3, "F").

CASE 2 (Fig. 4).—M. D., aged 66 years. This woman told of having suffered from heart trouble, shortness of breath and attacks of asthma for the previous five years. There was no history of rheumatism or syphilis.

Marked emphysema and bronchitis were present. The heart was enlarged; the sounds were weak but unaccompanied by murmurs; atrial fibrillation was present. Blood pressure, 145-100. Death occurred suddenly.

At necropsy the heart weighed 510 gm. The muscle cells showed moderate hypertrophy. There was a calcified area at the left edge of the mitral ring. In the aorta were numerous calcified plaques and the intima showed atheroma.

CASE 3 (Fig. 5).—B. B., colored, aged 40 years. This patient had been admitted several times during the previous two years. The clinical diagnosis was syphilitic myocarditis and nephritis. The heart was enlarged both to the left and to the right. There was a systolic murmur at the apex. Blood pressure, 140-115. The urine contained albumin and casts; the phenolsulphone-phthalein output for two hours was 30 per cent. Shortly after the last admission, Nov. 16, 1917, death occurred.

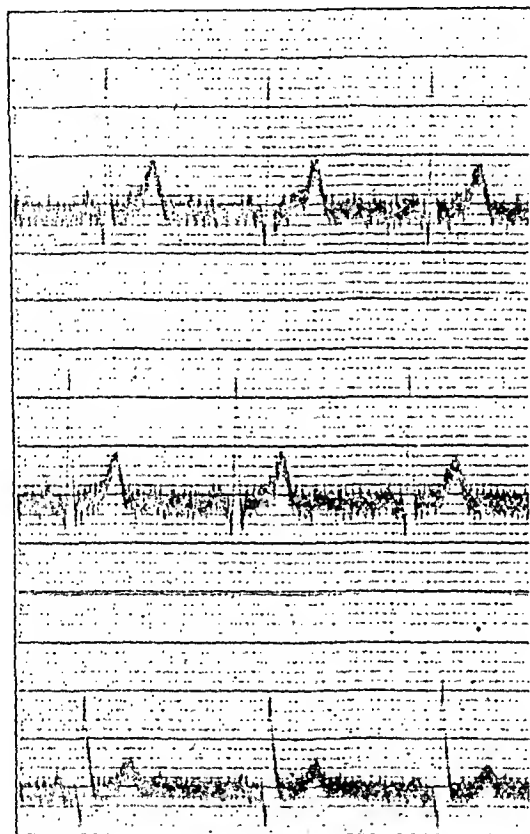


Fig. 10.—Case 28.

At necropsy, the heart weighed 785 gm.; the left heart was enlarged and the right heart distended. The papillary muscles were hypertrophied and sclerosed and there was a generalized fibrosis of the myocardium. The coronaries were thickened. The muscle elements showed hypertrophy and the striations could not be made out.

CASE 6 (Fig. 6).—M. A., colored, aged 50 years. This patient was admitted Oct. 11, 1917, and remained about six months. There was a history of repeated attacks of rheumatism and tonsillitis; she had several while in the hospital, and in addition, one attack of erythema nodosum. The tonsils were definitely pathologic. The heart was enlarged to the left, the left border being at the anterior axillary line; no murmurs were heard. The pulse was irregular in volume. Premature beats were present at different periods. Blood pressure, 168-98. The urine contained albumin and at times red and white blood cells.

CASE 7 (Fig. 7).—F. E., aged 57. This man had been seen several times during the previous two years. He suffered from attacks of dyspnea and occasional fainting spells. During recent months he had had numerous anginal attacks, with pain referred to the left arm. The heart was not enlarged to percussion. A systolic murmur was heard over most of the precordium. The aortic second sound was accentuated. Premature beats were present during every examination. Blood pressure, 118-75. The urine was negative.

CASE 10 (Fig. 8).—A. S., aged 42 years. On admission, the patient complained of shortness of breath and pain in the chest, of two months' duration. He had rheumatism twenty years previously and heart trouble nine years previously.

There was slight enlargement of the liver, and moderate edema of the ankles which disappeared promptly. The left border of cardiac dulness was at the midclavicular line; the right border, 3 cm. to the right of the sternal

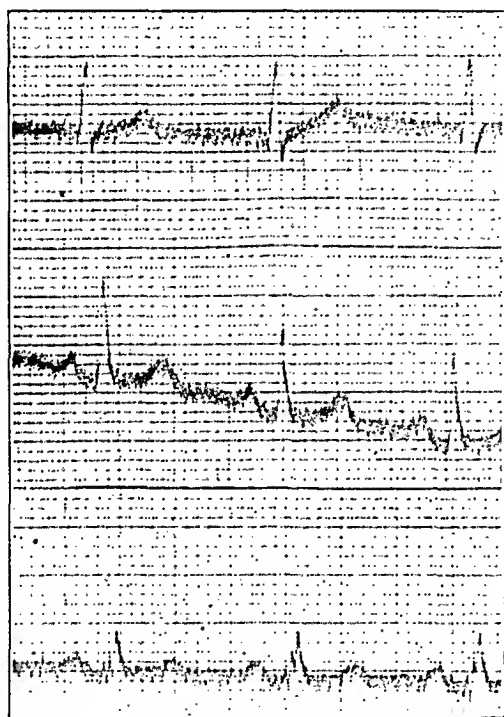


Fig. 11.—Case 26.

margin in the third and fourth spaces. The first sound at the apex was entirely replaced by a murmur which was transmitted to the axilla. Blood pressure, 110-70.

CASE 25 (Fig. 9).—J. Y., aged 43 years. While at work in a foundry the man became suddenly ill, with vomiting, abdominal cramps, diarrhea and pains in the muscles of the back and legs. Vomiting continued for several hours after he was brought to the hospital. Afterward he showed no symptoms during the six days he remained. He attributed his trouble to some pork that he had eaten for breakfast. The previous history was negative.

There was slight but persistent cyanosis. The knee jerks were sluggish; the examination of the nervous system was otherwise negative. The heart was not enlarged to percussion; the sounds were somewhat feeble; no murmurs were heard. The brachial and radial vessels were sclerosed. Blood pressure, 120-84 to 94. The urine contained a trace of albumin and hyaline and granular casts.

CASE 28 (Fig. 10).—N. R., aged 31 years. This man came into the dispensary complaining of headache, pains in the legs and transient tingling or prickling sensations in various cutaneous areas. There was a definite history of gonorrhea and of syphilis; no history of rheumatism.

The heart showed no enlargement and the sounds were normal except the aortic second which was distinctly accentuated. Blood pressure, 116-76. Blood Wassermann, two plus. Spinal fluid, negative.

CASE 26 (Fig. 11).—J. H., aged 38 years. This was a referred patient who was seen but once at the laboratory. He complained of attacks of palpitation at intervals of from six weeks to three months during the previous two years. These attacks occurred while at rest, usually at night. Simultaneously there was slight precordial pain, not referred to shoulder or arm, and without cutaneous hyperesthesia. He had suffered from asthma for the previous twelve years. There had been excessive use of chewing tobacco for twenty years.

The heart was not enlarged to percussion. The sounds were clear, not accentuated and unaccompanied by murmurs. The pulse rate was 78; the blood pressure, 132-80. Over the lungs occasional sibilant râles were heard and expiration was prolonged.

The first impression was that there was a large nervous element in this patient's distress. But the notching and slight prolongation of R in the third lead, and to a lesser degree in the second, of an otherwise almost normal electrocardiogram when considered in the light of other cases suggests greater myocardial involvement than is obvious from the physical signs and indicates a more plausible cause for those symptoms of which the patient complained.

St. Francis Hospital.

FATIGUE IN IRRITABLE HEART AND OTHER CONDITIONS *

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LAKEWOOD, N. J.

There is no more constant complaint among men suffering from the irritable heart of soldiers than that of fatigue. In civil life these men learned to adapt themselves to a low economic level by acquiring positions in which they could earn a living with the minimum of endeavor. Apparently the fatigue is of so real a nature to them that, to avoid it, they renounce most of the games and pleasures indulged in by the growing boy. In the army these men meet first their old enemy, physical exertion, without preliminary training, and with physique usually entirely inadequate to the demands. A considerable percentage do practically no duty, collapsing under the first "hike"; it is with this group that the work at Lakewood has largely dealt. Still others with this condition struggle through the training period, only to break down under the strain of battle conditions.

This work was undertaken with the purpose of finding some index to the degree or to the nature of this fatigue. Ryan¹ has observed that general fatigue exerts an influence on the white vasomotor reflex which is produced by stroking the skin with a blunt edged instrument. He showed that activity or loss of sleep causes a measurable shortening of the time interval between the appearance and fading of the white line that appears on the skin after such a stroke. Ryan constructed a simple spring instrument with which a stroke can be made by a blunt edge of wood under any desired pressure. His kindness in furnishing us such an instrument made this work possible.

The fatigue of which patients with the symptom complex of irritable heart complain is not limited to certain muscle groups. It is a general and frequently an overwhelming sensation. They often sit abject wherever they find themselves at the end of their exercises or throw themselves on their beds as soon as they can make their way to their wards. This study is concerned with general fatigue, and this symptom is largely responsible for the military disability of men with the irritable heart.

* From the U. S. Army General Hospital No. 9.

1. Ryan, A. H. (with the collaboration of J. H. Gordon): Proc. Soc. Am. Phys., December, 1917.

Ryan made his observations on five healthy nurses. He made readings of the duration of the vasomotor reflex at various times of day over a considerable period. He demonstrated that the duration time of the vasomotor reflex was shorter after a day's work than it was in the morning. He has, therefore, introduced this test as an index to general fatigue.

The white vasomotor reflex is well described by Longet,² who refers to previous observations by Marey.³ Longet describes the phenomenon as follows: "By stroking the skin with a blunt instrument, one sees first a white line from mechanical stripping; then, twenty or thirty seconds later, the white persistent line appears. This line differs from that made with a sharp instrument, which has a red center and white edges." This description agrees with the observations made at Lakewood, with the exception that the "latent period," the time between the stroke and the appearance of the persistent white line, has often been as short as ten seconds.

The nature of the phenomenon is not easy to determine. Vulpian⁴ says, "The phenomenon bears chiefly on the arterioles of the stimulated region, which are richly supplied with muscle fibers. These probably contract, forcing the blood into the capillaries. The capillaries then become blanched, being pressed on by the elasticity of the surrounding tissues, while no blood reaches them from the arterioles." Vulpian considered that, in addition to the muscular factor, the vasomotor apparatus is brought into play in the production of this phenomenon, because the appearance of the white line is not immediate. Whether there is a vasomotor element or not it is difficult to say, for the evidence from the literature does not carry us beyond the muscular factor. The effect of fatigue in shortening the duration of the line is probably exerted exclusively on the muscular apparatus, as nerve fibers are known to be unchanged by any stimulation short of the most prolonged, while smooth muscle is readily fatigued. Lee⁵ says, "While nerve is probably not indefatigable, it is extremely resistant in comparison with other peripheral tissues." The same writer⁶ tells us, from observations on skeletal muscle, that the depressing action of fatigue substance is exerted on the muscle protoplasm itself. Howell⁷ concludes that local fatigue is due to the elaboration of lactic acid, carbonic acid, and possibly acid potassium phosphate, and that the effect is probably due to the acidity of the products formed.

2. Longet, A.: *Traité de Physiologie* 2: 1869.

3. Marey: *Ann. des Sciences Nat. Zool.*, Series 4, 9:68.

4. Vulpian: *Physiologie et Pathologie du l'Appareil Vaso-Moteur*, p. 46.

5. Lee, F. S.: *J. A. M. A.* 46:1491 (May 19) 1906.

6. Lee, F. S., *Am. J. Physiol.* 20:170, 1907.

7. Howell: *Textbook of Physiology*, W. B. Saunders Co., Philadelphia and London, Ed. 7, 1918.

It seems, therefore, that we are dealing with a muscular or neuromuscular phenomenon of the peripheral vascular system, the duration of which is shortened following activity or loss of sleep, and that the direct cause of such shortening is probably the action of acid bodies on the vascular musculature.

While the test is local, it is affected by general bodily activity and is an index to the subject's sense of general fatigue.

The Test.—The test is performed in a darkened room. The subject exposes the anterior surface of the forearm, against which the concentrated rays of the 25 W. Mazda bulb are directed. A black background is very helpful, in resting the observer's eyes and in increasing the definition of the area to be observed. The Ryan instrument is grasped, and the wooden marking disk is pressed on the subject's forearm until the standard pressure (90 gm.) is indicated. This pressure was the same in all the tests. Then two strokes are made, without changing the pressure, across the forearm as rapidly as feasible. A stop watch is snapped at the end of the first stroke. At from ten to thirty seconds white lines appear where the strokes were made. The watch is snapped, read, and restarted, with the loss of only a fraction of a second. The first reading indicates the "latent period." As soon as the first indication of blushing of the white lines sets in the watch is again snapped: this second reading is the "duration time," and it is, according to Ryan, the more variable and significant figure.

By the foregoing technic the vasomotor phenomenon is practically always a pure white; in this respect it differs from the reaction obtained with a sharp instrument, when a red line is characteristically seen in the middle of the white reaction. In only one of several hundred tests made at Lakewood was a red vasomotor reaction (the common "tache") seen. In this instance the red line appeared in a few seconds, and no secondary white reaction could be seen; on repeating the test immediately after exercise a pure white reaction, of the usual type, was obtained. This observation was interesting, because it showed that there is a direct effect on the vasomotor system from even light general exercise.

Certain precautions were rigidly adhered to in performing this test, with the purpose of eliminating as far as possible the element of personal error in reading the reaction. If the observer is making a series of observations on the same individual, he should have no knowledge of previous readings; if he knows, for instance, that a reading of thirty seconds had been made an hour before he will unconsciously expect subsequent readings to be at about the same time. To avoid this, all the readings made at Lakewood were dictated to a clerk, who alone was aware of previous figures. The room in which the observations were made was always warm enough to prevent chilling; if the subject is not comfortably warm, the skin is not pink enough to show a satisfactory reaction. Moreover, a blanched skin is apt to be made pinker by exercise, and, if readings are made before and after exercise, an element of error is introduced on account

of the altered color of the skin. It was found that the test is very unreliable in the case of Jewish patients, probably on account of the usually sallow complexion of the skin, which furnishes an unfavorable background for the reaction. In the case of several men of this race no reaction whatever could be seen; in others, it was indistinct, and, in still others, the figures were so bizarre, that they must have been due to errors in reading the tests. For these reasons all figures obtained from tests on Jews were uniformly eliminated from the calculations here reported.

The Day Curve.—The first observations were on the day fatigue curve. Readings were made on fifty-four men at 8:30 a. m., 11 a. m. and 5 p. m. These men were all subject to similar routine. There were exercises before the first reading. There were also exercises at 4 p. m., but there was an average rest period of one hour between the afternoon exercises and the last reading. During the day the men were occupied with various light duties in the educational department, none of which was really fatiguing, and by walking or resting at their pleasure. The men for the test were taken from the cardiac wards. After the readings were made, they were grouped according to the clinical diagnoses of the patients, and the average days curves of the various groups of patients were calculated. They are shown in Chart 1. The diagnoses physically inferior, constitutionally inferior, emotionally sensitive, and neurotic are applied to groups of patients who have the syndrome of irritable heart; these subdivisions are based on suggestions made by Campbell⁸ from a study on the patients with cardiovascular disorders at this hospital. The organic group represents all patients with demonstrable organic disease of the heart. The post-infection group contains those patients who develop the symptoms of irritable heart after an acute infection, but in whom no organic disease of the heart can be demonstrated. Chart 1 shows nothing striking. There is a general correspondence among the curves; the more marked fatigue occurs between the latter two readings, except in the case of the group of physical inferiors. The most marked fatigue occurred in the emotionally sensitive group; this was again the case when readings were subsequently made just before and after exercise. In all groups the evening reading was shorter than the morning.

Fatigue by Exercise.—In order to make a quantitative estimate of the fatigue produced directly by physical exercise among men with irritable heart, readings were made in fifty-four cases just before and after exercise. The figures were again grouped according to clinical

8. Campbell: J. A. M. A. 71:1621, 1918.

diagnoses, and the results are shown in Chart 2. The first reading was made between 3 and 4 p. m.; at 4 o'clock the men had light "setting-up" exercises; at the end of which they reported for the second test. These results have particular bearing on the subject of fatigue in men with irritable heart. This general diagnosis includes Groups A, B, E, F, G and I in Chart 2. In Group K are two cases of hyperthyroidism with cardiac symptoms. The other groups are similar to the corresponding groups in Chart 1.

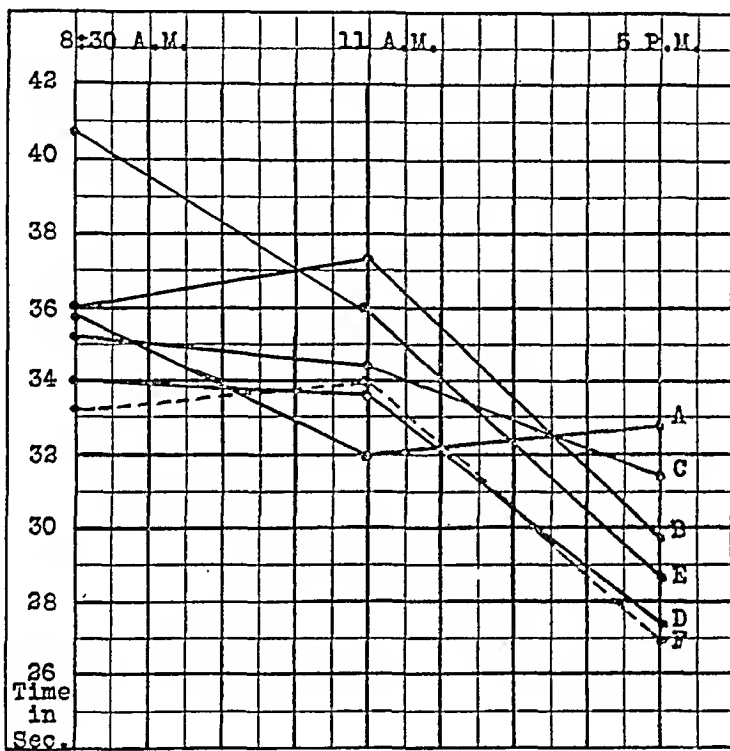


Chart 1.—Day curve of vasomotor reflex. A, physically inferior, eight cases; B, constitutionally inferior, seven cases; C, post-infection, twelve cases; D, organic, eighteen cases; E, emotionally sensitive, four cases; F, neurotic, five cases. Above are charted the average morning, midday and evening readings of the reflex of various groups of patients.

It will be seen from the chart that the two larger groups—the groups of the physically inferior and the constitutionally inferior—show definite fatigue of almost equal degree. Of sixteen men in these two classes, thirteen complained of fatigue from these light "setting-up" exercises. To avoid prejudice on the part of the observer, the readings were made before the men were interrogated as to their symptoms. It is, therefore, evident that patients belonging to either of these two groups do not imagine their fatigue; it has, apparently, a physical basis. From the general attitude of these men, one is

rather apt to feel that, as suggested by Lee,⁹ fatigue has "become a habit" with them. He says, "Our sensations become our servants or our masters, according as we will." There is no doubt that men of these classes are servants of their sensations, and that fatigue has

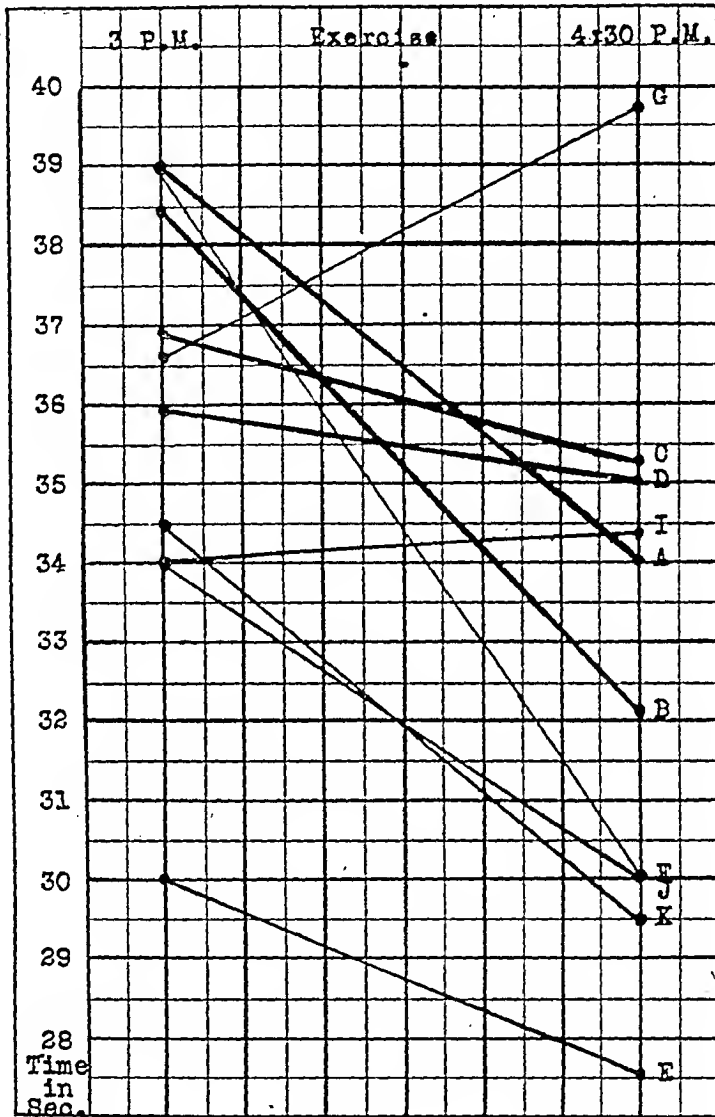


Chart 2.—Vasomotor reflex before and after exercise. A, physically inferior, five cases; B, constitutionally inferior, eleven cases; C, post-infection, ten cases; D, organic, fourteen cases; E, neurologic, two cases; F, emotionally sensitive, one case; G, chronic invalidism, three cases; H, neurotic, three cases; J, no disease, one case; K, hyperthyroidism, two cases.

become a habit, but it is illuminating to see that they actually suffer more fatigue than do their fellows of the organic and post-infection groups. The records of the smaller groups require no comment, except to point out that, here again, the emotionally sensitive group, as was the case in the day curve (Chart 1), shows the most marked

fatigue. Group G shows the "duration time" increased after exercise. Such a phenomenon is not uncommon in individuals who are physically strong. In this case the average reading after exercise was carried up by one that was nine seconds longer after exercise than before. The subject who showed this was an unusually powerful and active man; his symptoms were of purely psychoneurotic nature.

The organic and post-infection groups are much alike. The organic group may be considered a fairly satisfactory normal control, so far as fatigue is concerned, on the functional groups. All the men in the organic group had mild cardiac lesions well compensated. There was a striking correspondence between the sensations of these men and the readings of the vasomotor reflex. In the case of five men who did not complain of fatigue there was an average prolongation of the "duration time" of three seconds; eight men who complained of varying degrees of fatigue showed an average shortening of the time by three and one-half seconds. The neurologic group contains patients with irritable heart who have definite history or signs of organic neurologic disease, such as epilepsy. The group of the chronic invalids consists of men with the same symptoms as have all the other functional cardiac cases and who are chronic psychoneurotic patients with a history of chronic invalidism. The neurotic group contains men with the same symptoms, with somatic nervous phenomena, such as vomiting, frequent fainting, or excessive giddiness.

Why so many men with irritable heart have rapid fatigue is a problem which defies solution without further data. Lee⁹ says that "physical training . . . consists largely in the development of a power of resistance to the toxic fatigue substance." These men have not exercised in the past (most of them), and they have very little resistance to fatigue. The development of such resistance is probably not the least of the benefits which patients with irritable heart derive from graded exercises.

The Vasomotor Reflex and the Skeletal Musculature.—After the day curve of the vasomotor reflex had been observed in sixty-five men, it was thought that a comparison of these figures with the total muscle strength of the same men might prove of interest. This was done without regard to the nature of their various disabilities. The vasomotor reflex time was calculated by taking the average "duration time" of the three readings—morning, noon and evening. These figures are compared in Chart 3 with the strength to weight ratio of the same men. This ratio had been determined by Captain Bernard Smith and the writer. It was done by first estimating the total body strength by use of the Martin spring balance, and then dividing this figure by the weight of the individual. The resulting ratio represents

the total muscular efficiency of the individual. In Chart 3 the vasomotor reflex readings are arranged in sequence, from the longest "duration time" (46 seconds) to the shortest (20 seconds). The strength-weight ratio is indicated by the same scale. There is a general but definite relation between the "duration time" and the strength-weight ratio. The men with vasomotor reflex times of relatively long duration are the stronger men. This would seem to indicate that

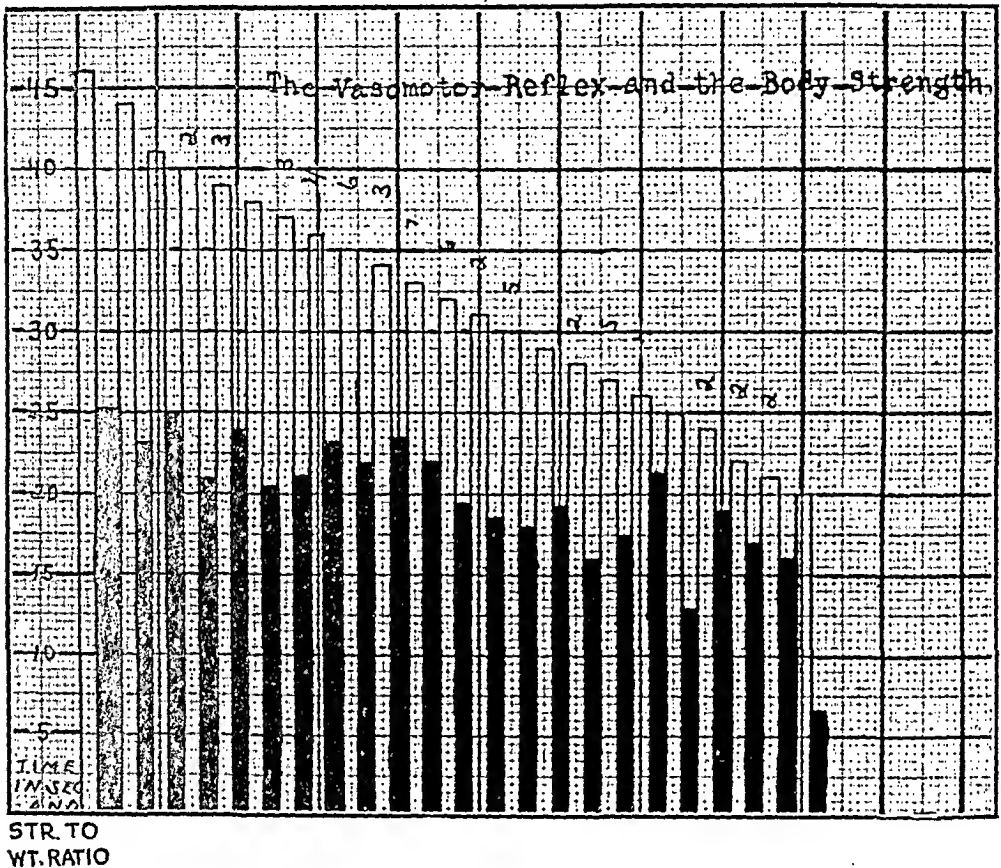


Chart 3.—The hollow blocks represent the vasomotor reflex, and the numbers over the columns indicate the number of men whose "duration time" is thus shown. The solid columns represent the strength-weight ratios of the same men grouped in the same order.

there is a correspondence between the strength of the arteriolar musculature and the skeletal musculature in a given individual.

The Convalescent Curve.—During the influenza epidemic the day curve of the vasomotor reflex was observed in the case of seven men, all of whom were in the first week of convalescence from uncomplicated influenza. These men had not yet returned to graded exercises or to educational work, although they were up and about their rooms. The curves are shown in Chart 4. The type of curve is characteristic and is unlike any of the normal day curves. This V-shaped curve is

uniformly present in the seven patients tested, except in the case marked 1 on the chart: this patient had the most severe illness of any and was out of bed for the first time. This probably accounts for the fact that he did not show recovery from fatigue in the afternoon, such as is shown by all the others. This rise in the "duration time" during the afternoon in the other men is difficult to explain. The morning seems to have caused fatigue in each case. The only difference

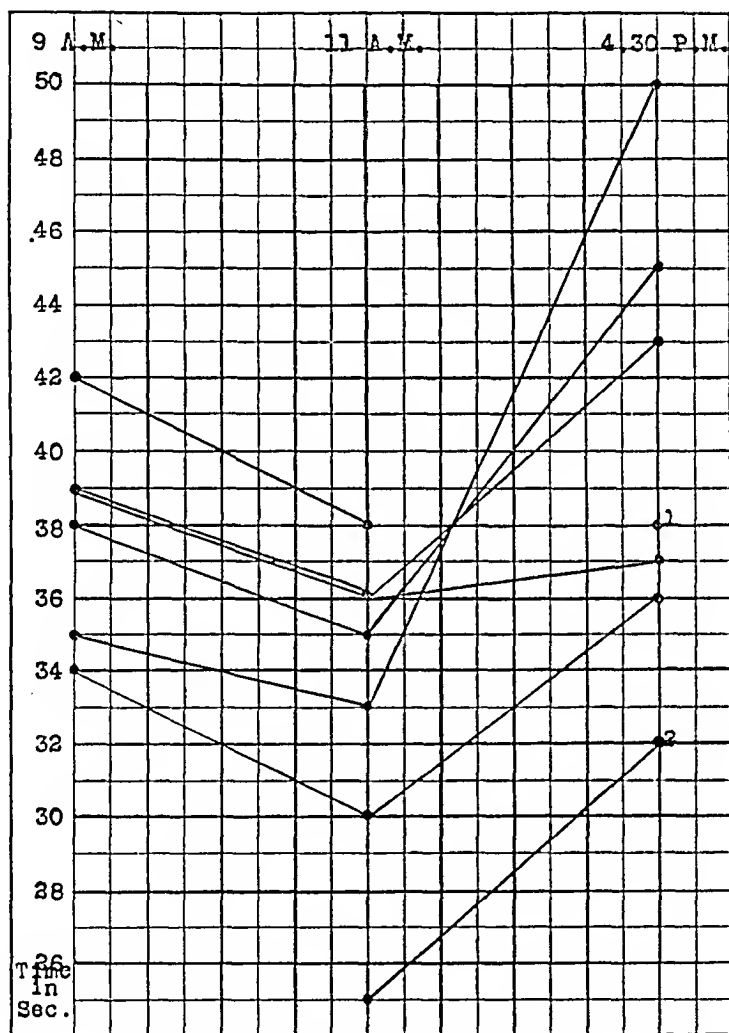


Chart 4.—Day curve in patients convalescent from influenza.

between the morning and afternoon routine of these men consisted in cleaning their rooms in the mornings, while the afternoons were devoted to absolute rest. Further observations on patients convalescent in bed should be made, as such a study might produce a method of determining the end of convalescence.

This work was done under the direction of Major Francis W. Peabody in the general study of the Irritable Heart of Soldiers at U. S. A. General Hospital 9, Lakewood, N. J.

CONCLUSIONS

1. The quantitative estimation of fatigue by the white vasomotor reaction, as suggested by Ryan, is of value in the study of clinical conditions. Owing to the various sources of possible error in the test, it is more suitable for group study than for individual cases.

2. The day curve of fatigue estimations is much the same in the several groups of cases that have the syndrome of irritable heart as in those with organic heart disease.

3. Patients with irritable heart who fall into the groups of general constitutional inferiority or pure physical inferiority show very rapid fatigue on exercise. This fatigue can be measured, and is an actual physical phenomenon and not of psychic origin.

4. There is a correspondence between the general body strength and the duration of the white vasomotor reflex. This suggests that there is a relationship between the strength of the skeletal musculature and the arteriolar musculature in a given individual. It is not considered, however, that the test is accurate enough to warrant estimating body strength from the vasomotor reflex in an individual case.

5. An unusual type of day fatigue curve, of V-shape, is usually found in patients convalescent from influenza. It is unlike the day curve obtained in any ambulant patient and may be characteristic of convalescence.

INFORMATION FOR AUTHORS OF MILITARY MEDICAL PAPERS

The circular on Medical Publications issued by the Surgeon-General's Office, March 27 and May 22, 1918, required (Paragraph 423, Manual of the Medical Department) that all medical manuscripts by medical officers, U. S. Army, intended for publication should be first submitted for approval to the Surgeon-General's Office, Washington, D. C. This regulation is still in force as far as medical officers on active duty are concerned. In the case of medical officers recently retired from active duty, in S. G. O. 700.7, issued March 20, 1919, it is requested, as a courtesy to the Surgeon-General and in aid of assembling material for the Medical History of the War, that all medical manuscripts based on military or official records or on military experience during the war, be submitted for record and approval, as heretofore, to the Secretary, Board of Publications, Surgeon-General's Office, Washington, D. C., and that such manuscript be accompanied by a carbon copy. On approval, the original copy will be forwarded for publication to the journal designated, and the carbon will be filed in the records of the Medical History of the War.

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CLINICAL SIGNIFICANCE OF BLOOD SUGAR IN NEPHRITIS AND OTHER DISEASES *

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First Paper

INTRODUCTION

Chemical examination of the blood is becoming more and more important in the clinical study of disease. Particularly is this true in those diseases in which the primary disturbance is one of perverted metabolism, of which diabetes mellitus and nephritis are the most common examples. The study of the sugar content of the blood in this field has attracted the attention of many workers, and there have appeared in the literature numerous contributions dealing with the significance of blood sugar and the various problems which it presents.

The studies thus far reported as to the clinical significance of blood sugar have been too few in number and too limited in character for the subject to be dismissed as one clearly elucidated. Moreover, certain methods of investigation have recently been proposed which appear to be worthy of statistical confirmation. For these reasons we propose in this study to present our observations and conclusions from a clinical study of blood sugar in a series of cases of diabetes, nephritis and other miscellaneous, but less important, disorders of body metabolism.

METHODS

In our studies on the sugar content of the blood, we have made use of the Myers¹ modification of the Lewis-Benedict² method for the determination of blood glucose. For the qualitative determination of urinary sugar, we have

* These studies were made in the Hahnemann Hospital, Rochester, N. Y., in which there is, under the direction of one of us, a hospital unit for the study of diseases of metabolism. This unit consists of a group of rooms in one ward and a well equipped special diet kitchen in charge of a trained dietitian. In conjunction with the hospital, there is a complete set of clinical and research laboratories, including a laboratory for work in pathologic chemistry.

† Working under the W. D. Ellwanger Fellowship in Pathological Chemistry.

1. Myers, V. C., and Bailey, C. V.: J. Biol. Chem. 24:147, 1916.

2. Lewis, R. C., and Benedict, S. R.: J. Biol. Chem. 20:61, 1915.

employed Benedict's³ Qualitative Solution, and to quantitate, we have made use both of the polariscope and Benedict's⁴ Quantitative Method.

The cholesterol determinations were made by Bloor's⁵ method (Bloor II, so-called). The blood urea was determined by Van Slyke and Cullen's⁶ modification of Marshall's urease method, while Folin's⁷ method was employed in our creatinin investigations. Our uric acid determinations were made by the Benedict-Hitchcock⁸ modification of the Folin-Macallum method, employing the technic recommended by Bogert.⁹

We used Van Slyke's¹⁰ apparatus for measuring the carbon dioxid combining power of blood plasma, and determined the carbon dioxid content of the alveolar air by means of the Frederica apparatus. We employed the Tycos instrument in obtaining our blood pressure values.

STUDIES ON NORMALS

Normal Blood Sugar Values.—Many workers have studied this interesting problem and have obtained varying results. These variations can be accounted for partly because of the methods employed and partly because some of the supposed "normals" were not normal. This is particularly true in the early work on this subject. Strouse¹¹ states that there are no fixed normal values for blood sugar, but that these vary within certain limits with individual peculiarities and diet. Hopkins,¹² using the Bang micromethod, obtained figures ranging from 0.06 to 0.11 per cent. with an average of 0.085 per cent. He quotes the work of Bing and Jacobsen, using the same method, who noted normal values of from 0.06 to 0.12 per cent. Gettler and Baker¹³ in their study of the blood in 30 normal individuals, employing the original Lewis-Benedict method, found the percentage of sugar varying from 0.05 to 0.11 per cent. Cummings and Piness,¹⁴ using a modification of the Lewis-Benedict micromethod of analysis, obtained much lower values, ranging from 0.04 to 0.12 per cent., with an average of 0.07 per cent. Myers and Bailey¹⁵ made observations on 500 cases, and state that most determinations made on individuals with no known cause for hyperglycemia show values from 0.09 to 0.11 per cent. and that a considerable number of hospital patients exhibit values from 0.12 to 0.14 per cent. Joslin¹⁶ speaks of normal values between 0.06

3. Benedict, S. R.: J. Biol. Chem. 5:485, 1909.

4. Benedict, S. R.: J. Biol. Chem. 9:57, 1911.

5. Bloor, W. R.: J. Biol. Chem. 24:229, 1916.

6. Van Slyke, D. D., and Cullen, G. E.: J. Biol. Chem. 19:219, 1914.

7. Folin, O.: J. Biol. Chem. 17:479, 1914.

8. Benedict, S. R., and Hitchcock, E. H.: J. Biol. Chem. 20:619, 1915.

9. Bogert, L. J.: J. Biol. Chem. 31:165, 1917.

10. Van Slyke, D. D., Stillman, E., Cullen, G. E., and Fitz, R.: J. Biol. Chem. 30:289, 1917.

11. Strouse, S.: Johns Hopkins Bull. 26:214, 1915.

12. Hopkins, A. H.: Am. J. M. Sc. 149:254, 1915.

13. Gettler, A. O., and Baker, W.: J. Biol. Chem. 25:217, 1916.

14. Cummings, R., and Piness, G.: Arch. Int. Med. 19:727, 1917.

15. Myers, V. C., and Bailey, C. V.: J. Biol. Chem. 24:152, 1916.

16. Joslin, E. P.: Treatment of Diabetes Mellitus, 1917, p. 727.

and 0.11 per cent., with most observations about 0.10 per cent. Dennis, Aub and Minot¹⁷ obtained values of from 0.85 to 0.11 per cent., using the Myers¹ modification of the Lewis-Benedict² method.

We also have endeavored to study the blood sugar values in normals. A series of thirty-nine young adults of both sexes in active life, who on careful physical and clinical examination appeared to be in good health, were selected for the blood-sugar tests. For purpose of emphasis, it may be said that all were urine sugar-free. The examinations were made at intervals of from one to six hours after the previous meal. The blood sugar values ranged from 0.07 to 0.15 per cent. In twenty-nine cases the values were 0.11 per cent. or less, while nine cases ranged from 0.12 to 0.14 per cent. One case had 0.15 per cent. The average of the series was 0.11 per cent. As a group there was no well marked relationship between the time of eating and the blood sugar level.

In addition to these, we have made observations on seventy-four other normals, the blood sugar values varying from 0.07 to 0.14 per cent., the average being 0.106 per cent. Thus we have examined in all, 113 normal individuals whose blood sugars averaged 0.107 per cent. Further, we have made blood sugar determinations on sixty miscellaneous cases not diabetes or nephritis, including gastro-intestinal disorders, pernicious anemia, etc. The range of values in these cases was from 0.07 to 0.16 per cent., with an average of 0.115 per cent. We have not sufficient data on any of these diseases to make an arbitrary statement as to the blood sugar findings, but it may be of interest that in four observations on two cases of cirrhosis of the liver, the readings were high normal or slightly elevated, varying from 0.12 to 0.16 per cent. In the light of Benedict and Lewis'¹⁸ statement that the blood sugar is increased in cancer, in five out of ten observations on nine cases of carcinoma, we found a moderate elevation, 0.12 to 0.16 per cent. In a series of twenty-two cases of miscellaneous infections, the range was from 0.07 to 0.15 per cent., with an average of 0.11 per cent.

BLOOD SUGAR IN NEPHRITIS

A number of workers have studied the blood sugar in nephritis. Hopkins,¹² using Bang's micromethod, studied a series of twenty-six patients, many of whom were evidently seriously ill. The blood sugar was normal in only five cases. The others showed a definite but moderate hyperglycemia.

In sixteen cases with a systolic blood pressure ranging from 180 to 280 mm. the blood sugar was normal in only five cases. The others

17. Dennis, W., Aub, J. C., and Minot, A. S.: *Arch. Int. Med.* 20:964, 1917.

18. Benedict, S. R., and Lewis, R. C.: *Med. Rec.* 77:650, 1914.

showed a definite but moderate hyperglycemia. In ten cases without high blood pressures, seven had normal blood sugars and three showed hyperglycemia. In the series the blood sugar ranged from 0.06 to 0.159 per cent.

Myers and Bailey¹ report a series of 33 blood sugar observations on 11 cases of severe nephritis. In 21 observations on 7 cases of interstitial nephritis (all fatal but one) the blood sugar ranged from 0.10 to 0.22 per cent. There was no glycosuria in these cases. In 10 observations on 10 cases of the parenchymatous type, the blood sugar varied from 0.14 to 0.20 per cent. These cases exhibited a mild glycosuria. In their experience generally, high blood sugar accompanied high urea, though in one case of parenchymatous nephritis with a blood sugar ranging from 0.17 to 0.20 per cent., the blood urea values were well within the normal limits, 22 mg. and 30 mg. per 100 c.c.

Myers and Killian¹⁹ in a report of twenty-three cases of nephritis state that the blood sugar values vary from 0.11 to 0.32 per cent., with an average of 0.157 per cent. They conclude that in general, high blood sugar values accompany high blood urea values.

Mason²⁰ states that the renal threshold is elevated in acute nephritis and reports that in one case after the ingestion of 100 gm. of glucose the blood sugar values in hourly periods were as follows: 0.10, 0.18, 0.217, 0.17 and 0.11 per cent. There was no urinary sugar.

We have studied in all 50 patients with cardiorenal disease, on whom we have made 88 blood sugar observations. The range of blood sugar levels was from 0.06 to 0.25 per cent., varying directly with the severity of the renal disease. Indeed, we are led to group our nephritis cases into three classes with reference to blood sugar content. In the early stages of interstitial or parenchymatous nephritis, when the general metabolism of the body is but little disturbed, blood sugars as a rule are normal. In the last stage of the disease, when the patient is in uremia, the blood sugar will be found very high, often equaling the blood sugar levels of severe diabetes. Other important metabolic constituents of the blood will also be found correspondingly increased, the whole presenting a picture of complete metabolic failure. A third group of cardiorenal cases, characterized by high blood pressure and little or no evidence of renal disturbance, usually exhibits high blood sugar levels. It is quite probable, as has been suggested by many workers, that some disturbance in the suprarenal bodies or other endocrinal glands is responsible both for the high blood pressure and the increased blood sugar. We were not able to throw light on this phase of the question. In general, it may be said

19. Myers, V. C., and Killian, J. A.: *J. Biol. Chem.* **29**:179, 1917.

20. Mason, E. H.: *Arch. Int. Med.* **21**:216, 1918.

that high blood sugar levels are associated with the severe phases of cardiorenal disease. These patients often excrete small quantities of sugar in the urine, although there appears to be no such quantitative relationship between food intake and urine sugar outgo as obtains in diabetes. Furthermore, the blood sugar level is inappreciably influenced by carbohydrate restriction in the diet. The practical significance of these facts is that such cases are often subjected to the discomfort of rigorous diabetic treatment, which is without effect either on the blood sugar level or the elimination of reducing substances in the urine.

TABLE 1.—COMPARISON OF BLOOD SUGAR LEVELS WITH OTHER CLINICAL DATA RELATING TO KIDNEY FUNCTION IN CASES OF CHRONIC DIFFUSE NEPHRITIS OF MILD AND MODERATE SEVERITY

No.	Sex	Age	Range of Blood Sugar, per Cent.	Range of Blood Pressure		Range of Blood Urea, Mg. per 100 C.c.	Phthalein Output, per Cent.	Ambard Coefficient
				Systolic	Diastolic			
1879	M	37	0.08-0.13	110-70	85-50	50-80	48	
2193	M	59	0.09-0.13	100-150	90	57-105	25	0.591
2270	M	30	0.10	180	120	86		
2438	M	52	0.11	160	100	118-123	25	0.461
2064	F	42	0.11	200	110	74		
2179	M	74	0.08	175	90	41		
2419	M	24	0.10	155-170	110-120	42-58	0.255
2220	M	13	0.10	115	80	50-77	0.127

TABLE 2.—COMPARISON OF BLOOD SUGAR LEVELS WITH OTHER CLINICAL DATA RELATING TO KIDNEY FUNCTION IN CASES OF CHRONIC DIFFUSE NEPHRITIS OF SEVERE TYPE

No.	Sex	Age	Range of Blood Sugar, per Cent.	Range of Blood Pressure		Range of Blood Urea, Mg. per 100 C.c.	Phthalein Output, per Cent.	Ambard Coefficient	Outcome
				Systolic	Diastolic				
1946	F	50	0.09-0.25	140-210	80-110	92-461	2.5-18	0.13	Dead
2143	F	46	0.13-0.20	180-240	100-140	188-277	3	0.68-2	Dead
2152	M	25	0.09-0.12	145-220	100-180	55-228	0.29-0.19	Dead
2156*	M	25	0.08-0.15	210-220	160-190	81-255	Dead
2243	M	45	0.18-0.20	170-180	90-105	353-492	Dead
2144	M	34	0.12-0.18	225	125	114-242	0.68	Dead
1690	M	54	0.14	130-180	70-130	89†	7-10	Dead
WC1	F	56	0.22	270	Dead
WC2	M	55	0.14	132-196	0.49	?

* This case separately discussed.

† Nonprotein nitrogen.

These patients (Table 1) were mildly sick clinically. It will be noted that the blood ureas and the Ambard coefficients of urea concentration are but moderately increased. Blood pressures, both systolic and diastolic, do not indicate a very serious disturbance. Blood sugar levels in each instance are normal. Disturbance in nitrogen metabolism precedes the rise in blood sugar.

These patients (Table 2) were all critically ill. In some instances the observations were made in the terminal stage of the disease. The high blood pressures, the severe albuminuria, extreme nitrogen reten-

tion, two-hour renal studies, high Ambard coefficients, etc., all indicate serious impairment of kidney function. In each of these cases the failure in nitrogen metabolism preceded the rise in the blood sugar level, the latter only becoming high in the critical stage of the nephritis.

These cases (Table 3) were all characterized by severe general edema, severe albuminuria, normal or moderately elevated blood pressures, little or no evidence of nitrogen retention and normal blood sugars. The high blood sugar determinations in cases 1669, 1960 and 1816 were obtained when the patients were moribund and probably represent terminal failure of metabolism.

TABLE 3.—COMPARISON OF BLOOD SUGAR LEVELS WITH OTHER CLINICAL DATA RELATING TO KIDNEY FUNCTION IN A SERIES OF CHRONIC PARENCHYMATOUS NEPHRITIS OF THE SEVERE TYPE

No.	Sex	Age	Range of Blood Sugar, per Cent.	Range of Blood Pressure		Range of Blood Urea, Mg. per 100 C.e.	Phthalein Output, per Cent.	Outcome
				Systolic	Diastolic			
2160	M	40	0.11	140-170	120-130	30-53	Dead
2226	F	23	0.11-0.11	150	100-105	39-55	59	Living
1669	M	59	0.14	180-225	100-130	67	23-55	Dead
2298	M	17	0.10-0.10	135	80	38-128	58	Living
2266	F	39	0.11	110-150	85-90	21-46	28	Living
1960	F	67	0.08-0.18	140-150	80	41-95	12	Dead
1816	M	54	0.13-0.20	210-240	130-160	64-92	22	Dead

TABLE 4.—COMPARISON OF BLOOD SUGAR LEVELS WITH OTHER CLINICAL DATA RELATING TO KIDNEY FUNCTION IN A SERIES OF CASES OF CARDIOVASCULAR DISEASE

No.	Sex	Age	Range of Blood Sugar, per Cent.	Range of Blood Pressure		Range of Blood Urea, Mg. per 100 C.e.	Phthalein Output, per Cent.	Outcome
				Systolic	Diastolic			
2110	F	52	0.12	200	100	45	Living
2170	F	73	0.10	160-200	85-100	38	Living
1829	M	51	0.12	170-200	100-120	40	41	Living
1853	F	56	0.11	200-240	110-120	31-40	Living
2263	M	44	0.12-0.13	180-210	110-140	30-43	Living
1429	M	51	0.11	180-220	130-150	40-56	22-30	Dead
2176	M	53	0.10-0.15	150-180	120	23-61	Dead
2358	F	54	0.11	200-220	130-140	40-77	23	Living
2398	M	48	0.11	200-230	140-170	37-79	14-13	Living
2154	M	63	0.10	160-180	80-100	31-45	Living
1988	F	60	0.10	68	35	Living
2225	M	66	0.10	190-240	83	Living
1633	F	49	0.12	140-190	100-120	34	46-70	Living
2440	F	54	0.12-0.23	170-220	115-140	43-19	46-70	Living
2185	M	53	0.20	160	90-110	41-51	43	Living

These cases (Table 4) are characterized by very severe hypertension, slight or no albuminuria, and little or no nitrogen retention. They all exhibit normal blood sugars except case 2176, in which the high observation was made when the patient was moribund, and cases 2170, 2185 and 2440, whom we believe from other clinical evidence to have some endocrinal disturbance. Case 2440 we have studied in detail. Clinically, Cases 2110, 2263, 1829 and 1633 seem to be in the early stages of this same endocrinal type.

TABLE 5.—CASE 1946. COMPARATIVE BLOOD ANALYSES IN A FATAL CASE OF CHRONIC DIFFUSE NEPHRITIS IN THE BEGINNING AND TERMINAL STAGES

Date 1917	Blood Analysis					Urine Analysis		Diet			
	Urea, Mg. per 100 C.e.	Creatin, Mg. per 100 C.e.	Cholesterol, Mg. per 100 C.e.	Ambard Coeffi- cient	Sugar, per Cent.	Sugar	Albu- min	Pro- tein, Gm.	Fat, Gm.	Car- bohy- drate, Gm.	Calo- ries
6/12 1918	99.4	10.2	189	0.13	0.09	0	+++	30	77	157	1,471
4/11	348.9	10.0	0.15	0	++	33	22	74	(68)
4/12	323.2	11.1	158	0.25	0	++	33	22	74	680
4/18	460.5	16.1	0.25	0	0	33	22	74	680

CASE 1 (No. 1946).—Woman, aged 50; nephritis, probably of less than one year's duration. Blood pressure at time of first examination, systolic 150 mm., diastolic 90 mm. Clinical symptoms at first comparatively mild with moderate elevation of blood urea and normal blood sugar. High blood creatinin portended fatal outcome. The blood analyses made ten months later and just before death reveal a severe failure of nitrogen metabolism and an accompanying rise in blood sugar. It is noteworthy that nitrogen retention preceded the failure in sugar metabolism. The patient's urine was sugar-free. The renal blood sugar threshold in this case was more than 0.25 per cent. (Table 5).

TABLE 6.—CASE 2144. COMPARATIVE BLOOD ANALYSES IN A SEVERE CASE OF CHRONIC DIFFUSE NEPHRITIS

Date 1917	Blood Analysis					Urine Analysis			Diet			
	Urea, Mg. per 100 C.c.	Creat- inin, Mg. per 100 C.c.	Choles- terol, Mg. per 100 C.c.	Ambard Coeffi- cient	Blood Plasma CO ₂ , C.c. per 100 C.c.	Sugar, per Cent.	Sugar	Albu- min	Pro- tein, Gm.	Fat, Gm.	Car- bohy- drate, Gm.	Calo- ries
9/17	242.0	8.8	128	40.9	0.18	0	+++	32	32	64	640
9/25	114.2	10.6	160	0.68	30.0	0.14	0	+++	38	38	76	760
9/27	12.2	30.0	0.12	0	+++	32	32	64	640

CASE 2 (No. 2144).—Man, aged 34; nephritis of seven years' standing. Blood pressure, systolic 225 mm., diastolic 120 mm. On admission to hospital there was severe general edema and dyspnea. Blood examinations showed evidence of extreme metabolic failure in the high urea and sugar. High creatinin and low plasma carbon dioxid portended fatal outcome. On Karrell diet, noteworthy clinical improvement with disappearance of edema and dyspnea accompanied by a sharp decline in blood urea and sugar. Patient left hospital in good condition but succumbed to pneumonia one month later (Table 6).

CASE 3 (No. 1816).—Man, aged 54; clinical evidence of severe arteriosclerosis over a period of two years. Blood pressure, systolic ranging from 220 to 250 mm., diastolic 110 to 140 mm. Data in Table 7 represents the terminal stage of the disease. Attention is called to the slight nitrogen retention and the slightly elevated blood sugars. At the time of the last test, the patient was critically ill, edema and dyspnea were very pronounced. This case illustrates the probable degree of metabolic failure in the terminal stage of chronic parenchymatous nephritis.

CASE 4 (No. 2156).—Man, aged 25; had been a chronic alcoholic for eight years; admitted to hospital in delirium and coma two weeks before death. Blood pressure, systolic 210 mm., diastolic 160 to 190 mm. Note (Table 8) the comparatively slight failure of nitrogen metabolism on admission and the rapid change to a condition of marked retention before death. These findings are paralleled by the blood sugar curve. The absence of severe acidosis as

shown by the blood plasma curve is noteworthy in this case. Necropsy findings: The kidneys presented very little gross evidence of disease. On section there was a moderate degree of connective tissue in the cortex, some sclerosis of the blood vessels and a little patchy calcification in the tubules. The medullary rays were but a little affected. The brain was extremely edematous and hemorrhagic.

TABLE 7.—CASE 1816. COMPARATIVE BLOOD ANALYSES IN A PATIENT WHO, IN THE EARLY STAGES OF THIS STUDY, PRESENTED CLINICAL EVIDENCE OF GENERAL ARTERIOSCLEROSIS AND RENAL SCLEROSIS, LATER DEVELOPING SIGNS OF PARENCHYMATOUS NEPHRITIS WITH SEVERE ALBUMINURIA AND EDEMA AND SLIGHT NITROGEN RETENTION. FATAL TERMINATION THREE MONTHS AFTER LAST ANALYSIS

Date 1917	Blood Analysis						Urine Analysis		Diet			
	Urea, Mg. per 100 C.c.	Creat-inin, Mg. per 100 C.c.	Uric Acid, Mg. per 100 C.c.	Ambard Coeffi- cient	Blood Plasma CO ₂ , C.c. per 100 C.c.	Sugar, per Cent.	Sugar	Albu- min	Pro- tein, Gm.	Fat, Gm.	Car- bohy- drate, Gm.	Calo- ries
10/16	67.21	4.2	0.24	48.1	0.14	0	+++	32	32	64	640
10/25	65.78	3.6	7.97	53.2	0.14	0	+++	39	38	134	1,031
11/ 5	64.64	2.5	6.90	0.13	0	+++	67	75	136	1,176
11/19	92.95	50.9	0.20	0	+++	61	126	225	2,202

TABLE 8.—CASE 2156. COMPARATIVE BLOOD ANALYSES IN A FATAL CASE OF CHRONIC ALCOHOLISM AND CHRONIC DIFFUSE NEPHRITIS

Date 1917	Blood Analysis						Urine Analysis		Diet			
	Urea, Mg. per 100 C.c.	Creat-inin, Mg. per 100 C.c.	Uric Acid, Mg. per 100 C.c.	Choles- terol, Mg. per 100 C.c.	Blood Plasma CO ₂ , C.c. per 100 C.c.	Sugar, per Cent.	Sugar	Albu- min	Pro- tein, Gm.	Fat, Gm.	Car- bohy- drate, Gm.	Calo- ries
10/16	80.8	2.8	192	52.8	0.08	0	++++	16	16	32	320
10/19	82.9	3.7	48.1	0.10	0	++++	25	25	68	580
10/24	254.5	6.2	13.0	50.3	0.15	0	++++	6	0	0	30
10/27	230.2	7.0	50.5	0.15	0	+	5	2	19	99

TABLE 9.—CASE 2143. COMPARATIVE BLOOD ANALYSES IN THE TERMINAL STAGES OF A FATAL CASE OF CHRONIC DIFFUSE NEPHRITIS

Date 1917	Blood Analysis							Urine Analysis		Diet			
	Urea, Mg. per 100 C.c.	Creat- inin, Mg. per 100 C.c.	Uric Acid, Mg. per 100 C.c.	Choles- terol, Mg. per 100 C.c.	Ambard Coeffi- cient	Blood Plasma CO ₂ , C.c. per 100 C.c.	Sugar, per Cent.	Sugar	Albu- min	Pro- tein, Gm.	Fat, Gm.	Car- bohy- drate, Gm.	Calo- ries
9/29	188.8	6.2	38.5	0.14	0	+++	32	32	64	640
10/ 3	9.1	11.2	240	32.3	0.16	0	++	32	32	64	640
10/ 4	140.1	8.9	11.5	...	0.68	34.3	0.13	0	++	32	32	64	640
10/11	231.7	13.9	13.2	201	1.99	29.1	0.19	0	+++	39	37	107	903
10/19	277.4	12.8	24.1	0.20	0	++++	2	1	54	436

CASE 5 (No. 2143).—Woman, aged 46; blood pressure, systolic 230 mm., diastolic 140 mm.; extensive edema; severe dyspnea. The failure of nitrogen metabolism (Table 9) was more serious and preceded the failure in sugar metabolism. High renal blood sugar threshold. Necropsy findings: kidneys, gross examination, small, contracted. On section the cortex exhibited an extreme degree of fibrosis and granulation tissue which had obliterated a

generous percentage of the parenchymatous structures. Many of the glomeruli were scarred while those remaining had a varying degree of sclerosis in the tufts. The dilated convoluted tubules contained degenerate necrotic epithelium. The blood vessels showed an extreme grade of hyaline necrosis, particularly in the intima, almost to the point of obliteration. Marked cloudy swelling and fatty degeneration of the liver and suprarenal bodies were present.

CONCLUSIONS

1. The average digestion blood sugar level in 113 normal individuals was 0.107 per cent., the values ranging from 0.07 to 0.14 per cent.

2. The range of the blood sugar level in a series of sixty cases of miscellaneous diseases, chiefly gastro-intestinal disorders and pernicious anemia, excluding diabetes, nephritis and infections, was from 0.07 to 0.16 per cent., with an average of 0.115 per cent.

3. In a series of nine cases of carcinoma there was a moderate elevation of blood sugar, 0.12 to 0.16 per cent.

4. In a series of twenty-two miscellaneous infections, chiefly influenza, pneumonia, and streptococcus, the range was from 0.07 to 0.15 per cent., with an average of 0.11 per cent.

5. In the early stages of nephritis, when the general metabolism of the body is but little disturbed, blood sugars, as a rule, are normal.

6. In the last stages of nephritis, when the patient is in uremia, the blood sugar will be found very high, often equalling the severe stages of diabetes. Other important metabolic constituents of the blood will be found correspondingly increased, presenting a picture of complete metabolic failure.

7. A third group of cardiovascular cases, characterized by high blood pressure and little or no evidence of renal disturbance, usually exhibits blood sugar levels slightly higher than normal.

8. In severe cases of nephritis, patients may excrete small quantities of sugar in the urine, frequently giving rise to the misapprehension that true diabetes exists. In such cases the blood sugar level is inappreciably influenced by carbohydrate restriction, and these patients should not be subjected to the discomfort of rigorous diabetic diet.

9. Failure in nitrogen metabolism precedes, often by months, the rise in blood sugar, so that the latter has a rather serious prognostic omen.

THE CLINICAL SIGNIFICANCE OF BLOOD SUGAR IN DIABETES MELLITUS

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Second Paper

We have studied the blood sugar levels in 127 cases of diabetes, fifty-six males and seventy-one females, making in all 1,106 blood sugar determinations. In our study of the renal threshold for sugar in diabetes, we found no constant blood sugar level for the appearance of urinary sugar. Hopkins¹ says that there is no constant renal threshold. Hamman and Hirschman² found the normal threshold between 0.17 and 0.18 per cent., and our own findings would seem to corroborate this. In diabetes, however, we may find a lowering or an elevation of the threshold. In the former case, the blood sugar level may be very slightly lowered or may approximate normal values. We now have under observation several patients who persistently show reducing substances in the urine accompanied by low blood sugar values. Some of these cases may prove to be cases of alimentary glycosuria or renal diabetes. We cannot say in diabetes whether the threshold remains the same for any length of time. We are sure, on the other hand, that it may vary widely with changes in the condition of the patient. We have noted an elevation of blood sugar in cases of diabetes complicated by nephritis, and particularly in certain diabetics, who, from mild or moderately severe stages of the disease, have developed into that more serious stage accompanied by acidosis and frequently by cholesterinemia. These cases are characterized by high blood sugar levels as will be shown presently.

It is important at this time to distinguish between blood sugar level and renal threshold since both expressions are used frequently throughout this paper. A diabetic on a very liberal diet may have a high percentage of sugar in his blood and at the same time be eliminating large amounts of sugar in his urine. The height of the blood sugar level at which he ceases to eliminate appreciable quantities of glucose is considered his renal threshold for sugar. This figure may be considerably below his highest blood sugar level. Thus, in one of our cases, the patient on admission to the hospital had a blood sugar level of 0.67 per cent., but his threshold later proved to be 0.17 per cent.

1. Hopkins, A. H.: Am. J. M. Sc. 149:254, 1915.

2. Hamman, L., and Hirschman, I. I.: Arch. Int. Med. 20:761, 1917.

We have attempted to study the effect of the duration of the diabetes on the renal threshold. The analysis of this study is seen in Table 1, in which the total number of cases showing different approximate threshold percentages is given.

TABLE 1.—SHOWING EFFECT OF DURATION OF DIABETES ON RENAL THRESHOLD FOR SUGAR

Duration of Disease, Years	Blood Sugar Renal Threshold, per Cent.					Total Number of Cases
	0.15	0.17	0.19	0.24	0.25	
Less than 1.....	2	1	6	5	..	14
1 to 2.....	2	..	8	4	..	14
2 to 3.....	..	1	4	6	..	11
3 to 5.....	1	2	4	2	1	10
5 to 10.....	..	1	3	5	1	10
10 to 15.....	..	1	2	2	..	5
15.....	1	1
Total number of cases...	5	6	27	24	3	65

In Table 1 it will be seen that two patients who had diabetes for less than one year had thresholds under 0.15 per cent. Six cases with diabetes of less than one year's standing had thresholds of less than 0.19 per cent., but more than 0.17 per cent., and so on. A cursory examination of the foregoing data leads one to the impression that there is no striking relation between the duration of the disease and the height of the renal blood sugar threshold. We feel, therefore, that this data should be interpreted in the light of our clinical experience. These studies are based on observations made in the hospital over a period averaging four weeks. Some few cases which were under observation for longer periods showed a comparatively rapid rise in threshold. Apparently when diabetes is mild or quiescent, the blood sugar threshold is stationary, but when the disease becomes progressive, the threshold tends to rise. Indeed, before death the blood sugar threshold may reach great heights with little or no sugar appearing in the urine. A rising renal threshold for sugar, therefore, in the face of careful dietary treatment, is a serious prognostic sign.

We have had an opportunity to study several cases illustrating this point and will cite three.

CASE 1.—Woman, aged 28. Fatal diabetes; under observation five months; early blood sugar renal thresholds 0.16 and 0.18 per cent.; in terminal stages, 0.20, and 0.25 per cent.

CASE 2.—Woman, aged 18. Fatal diabetes; under observation two and one-half years; early blood sugar renal thresholds 0.19 and 0.20 per cent.; in terminal stage, blood sugar thresholds 0.25 and 0.30 per cent.

CASE 3.—Woman, aged 22; severe diabetes; living; under observation six months; early thresholds below 0.18 per cent.; present threshold 0.20 and 0.25 per cent.; declining food tolerance.

The severity of the diabetes is therefore important in any consideration of blood sugar renal threshold. High thresholds are rarely seen in mild diabetes. When present, they usually mean some complications, as arterial hypertension. It is difficult to determine the threshold in mild cases, as a rule, because they yield readily to treatment and the opportunity for sufficient observations is not afforded. High thresholds are often found in mild cases in which the patients are on unrestricted diets. When a high threshold is found in mild uncomplicated diabetes, it is usually because the patient is eating very liberal diets, whereas in severe diabetes with a high threshold, the diet is usually low. The high threshold may mean a physiologic expedient to conserve food material. Mosenthal³ expressed the view that a high blood sugar was a protective measure, but our experience indicates that persistent high blood sugar levels promote exhaustion and rapid decline of function, and the high threshold is merely a safety measure. Furthermore, in severe cases where extremely low diets are necessary to maintain life, the high threshold is essential to take care of the seriously impaired carbohydrate metabolism. Our experience has led us to the conclusion that it is desirable to maintain the blood sugar level as nearly normal as possible even though severe restrictions in diet may be necessary for this purpose, notwithstanding the fact that in most cases the high threshold will permit of a much more liberal diet without the appearance of sugar in the urine. We regard this as the cardinal feature in the successful treatment of diabetes, and look with misgiving and apprehension on any plan of treatment which permits of food just short of the point of glycosuria.

TABLE 2.—RELATION OF BLOOD SUGAR RENAL THRESHOLD AND SEVERITY OF DIABETES

Degree of Severity	Blood Sugar Renal Threshold, per Cent.					Total Number of Cases
	0.15	0.17	0.19	0.24	0.25	
Mild.....	2	2	7	8	..	19
Moderately severe.....	3	1	2	8	2	16
Severe.....	1	3	15	12	3	34
Total number of cases...	6	6	24	28	5	69

It is our practice to make blood sugar determinations with every change in diet, and at least as often as every three days.

An analysis of sixty-nine cases of diabetes arranged to show the relation of blood sugar renal threshold and the severity of diabetes will be found in Table 2.

The age of the patient is undoubtedly a factor in the determination of the renal blood sugar threshold. Younger diabetics as a rule

3. Mosenthal, H. O., Clausen, S. W., Hiller, A.: Arch. Int. Med. **21**:93, 1918.

have low or normal thresholds. As age advances, the threshold rises. This may partly be explained by the frequently occurring complications of renal and endocranial involvement (Table 3).

TABLE 3.—AGE AND RENAL BLOOD SUGAR THRESHOLD

Age, Years	Blood Sugar Renal Threshold, per Cent.					Total Number of Cases
	0.15	0.17	0.19	0.24	0.25	
1 to 9.....	1	2	2	5
10 to 19.....	1	1	4	2	..	8
20 to 29.....	7	3	..	10
30 to 39.....	1	2	4	3	..	10
40 to 49.....	1	1	3	4	3	12
50 to 59.....	4	8	..	12
60 to 69.....	2	3	..	5
70 to 79.....	1	2	..	3
Total number of cases...	4	6	27	25	3	65

INTERPRETATION OF CHARTS

The accompanying charts are plotted to show the relation of the height of blood sugar to other important clinical phenomena of diabetes, and especially to the severity of the disease. In general, the charts show the relation of food intake, body weight, carbon dioxid tension of alveolar air, blood sugar per cent., and urine sugar outgo. It will be noted that the food intake is plotted in calories, the key on the left border revealing the meaning of the different types of hatching. Food intake is thus plotted because the different elements of the diet are additive and the total intake as well as proportions of the various elements may thus be determined at a glance. The carbon dioxid tension of the alveolar air is plotted as the index to acidosis, although in the studies frequent determinations of the blood plasma carbon dioxid have been made as controls, using Van Slyke's⁴ well known method. Readings below the line marked "normal minimum" indicate acidosis. Blood sugar is plotted in terms of per cent. It is assumed that above 0.15 per cent. is abnormally high; thus this line for purpose of ease in study is made bold faced. Urine sugar outgo is plotted in calories so that the carbohydrate balance of a case may be ascertained by comparing intake with outgo.

Chart 1.—Case 1936. Before admission to the hospital this little boy was examined by the authors and found to have 6.6 per cent. of sugar in the urine. He also presented the usual clinical symptoms of diabetes, as thirst, polyuria, weakness, and loss of weight. Except on occasions when he has had some infection, his blood sugar has remained remarkably low. Thus, when the test was made, Oct. 16, 1917, he had a severe bronchitis. The test on Dec. 5, 1918, was made three days after the removal of the tonsils. This child is

4. Van Slyke, D. D., Stillman, E., Cullen, G. E., and Fitz, R.: *J. Biol. Chem.* 30:289, 1917.

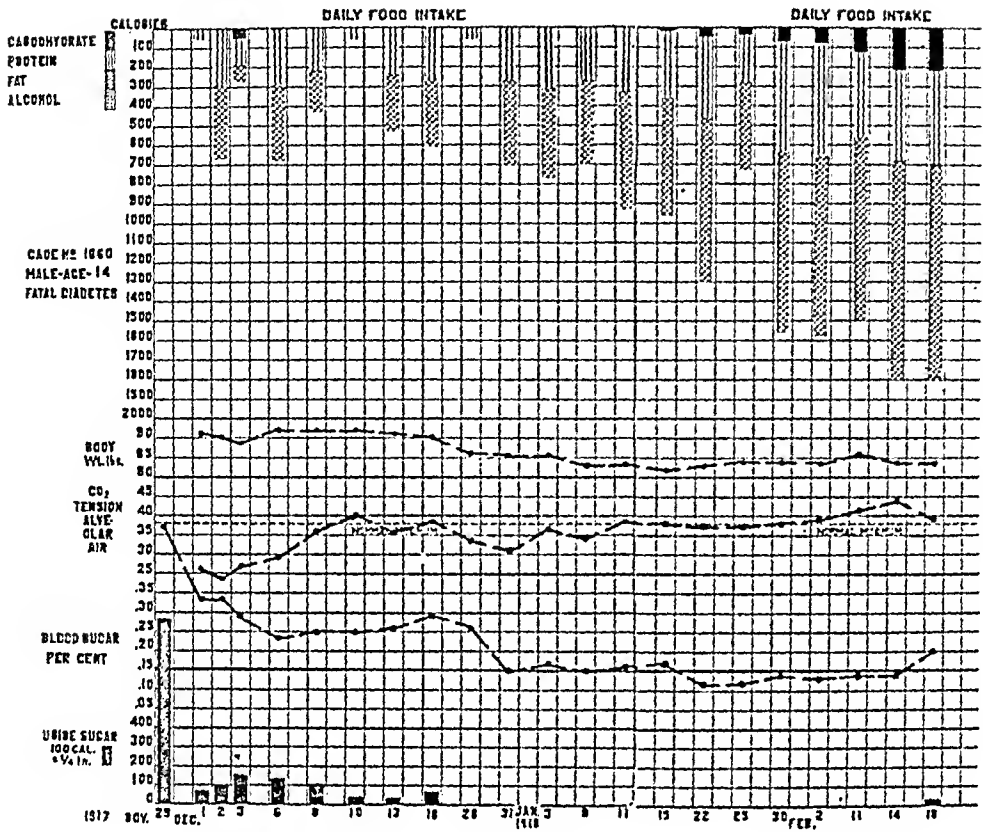


Chart 1

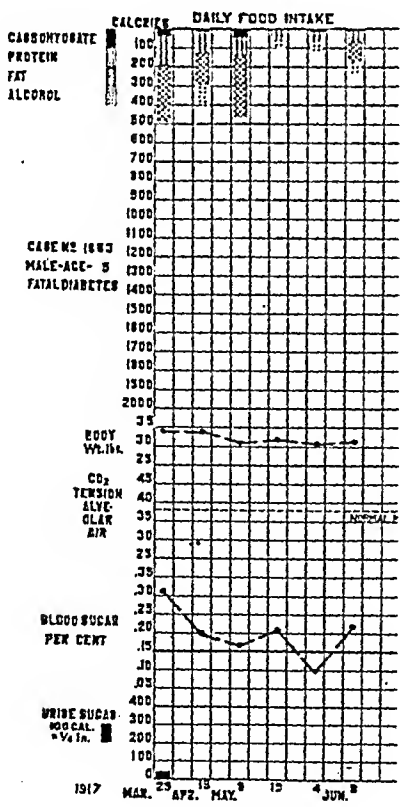


Chart 2

growing slowly and gaining weight steadily. The lowness of his blood sugar curve attests to the mildness of his diabetes and his response to treatment. In our experience; a persistent low blood sugar curve in a child is an extremely favorable prognostic sign.

Chart 2.—Case 1883. This little 5-year-old child first presented symptoms of diabetes about one month before entering the hospital. He was under continuous observation for sixteen weeks. It was quite impossible to keep him urine sugar-free on the most rigorous diets. Only a portion of his metabolism record is here shown. It was noteworthy that he had a persistent high blood sugar curve and an absence of acidosis except at the end. Acidosis in this case was measured by urinary ammonia output and is not here shown. In the favorable cases in children which we have studied, blood sugar levels are usually low.

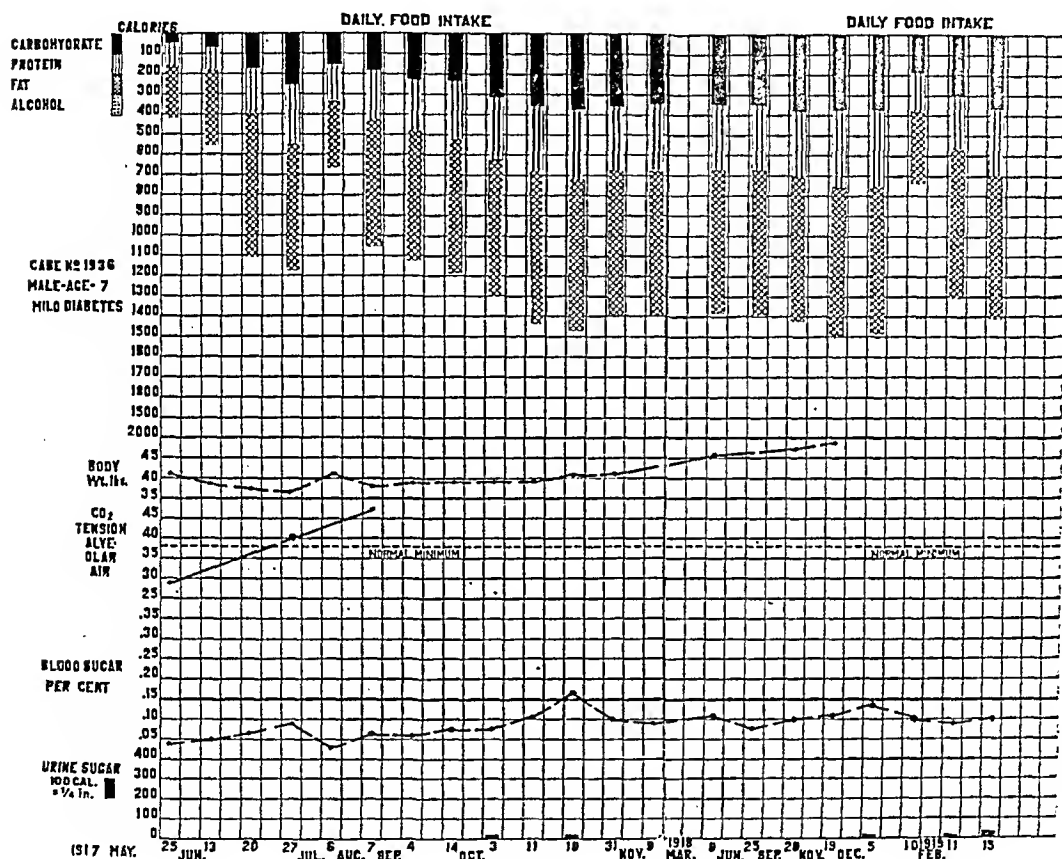


Chart 3

Chart 3.—Case 1660. This boy had severe diabetes for more than two and one-half years. When admitted to the hospital he was in extreme acidosis and had a very high blood sugar, as will be observed. He also had a very high blood cholesterol. It was with great difficulty that his blood sugar level was reduced, this being accomplished by alternating fasting and underfeeding. He was finally discharged in good condition and on a fairly liberal diet. A few months later he committed excesses in eating and rapidly succumbed in coma.

Chart 4.—Case 2288. This patient has had severe diabetes for the past four years. She is emaciated and presents the usual clinical picture of an individual who has undergone prolonged undernourishment. On admission to the hospital and while on a very low diet, she had a persistent high blood sugar which was difficult to reduce; but by persistent underfeeding and particularly by keeping the carbohydrate intake low, usually less than 10 gm., and

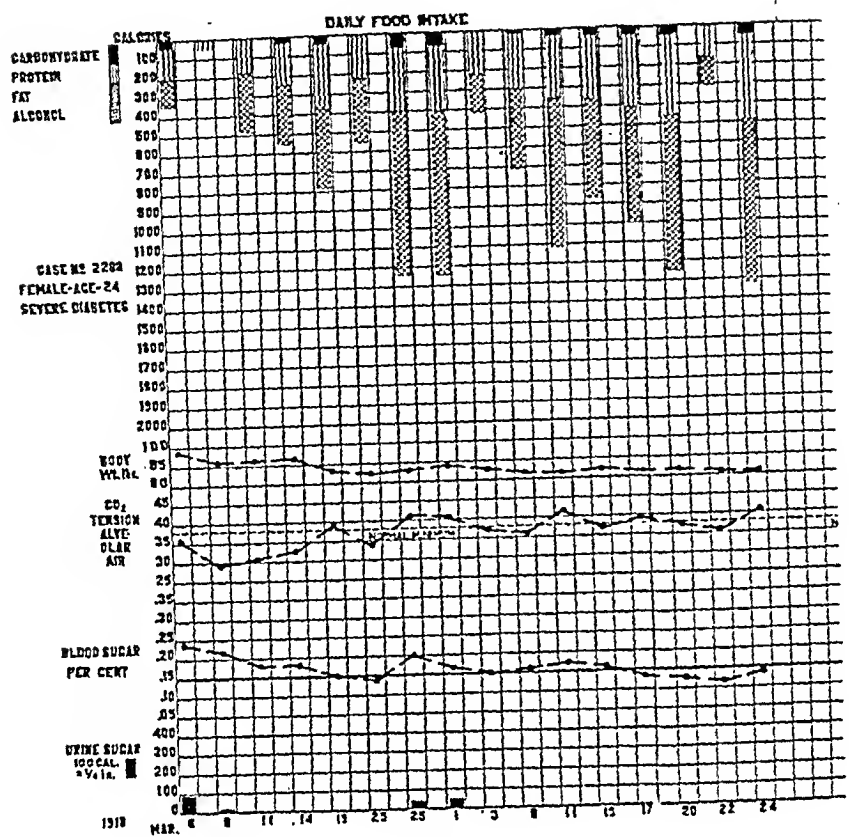


Chart 4

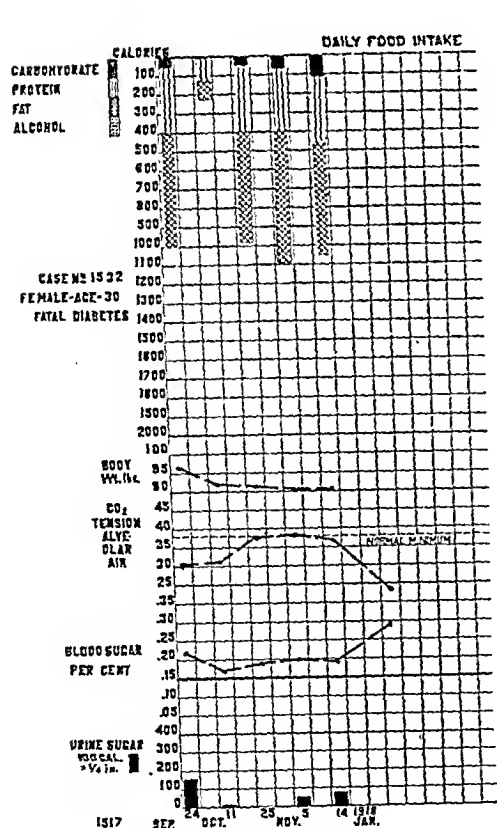


Chart 5

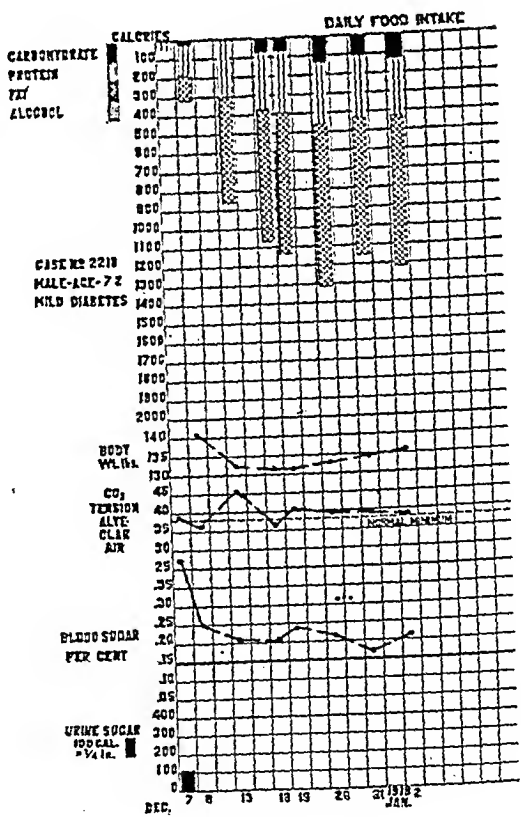


Chart 6

often none, her blood sugar level was reduced to between 0.12 and 0.15 per cent. The patient has remained on this low diet for more than one year and is doing fairly well.

Chart 5.—Case 1532. This patient first came under observation in September, 1915, shortly after the onset of her diabetes. For the first few months, there was no difficulty in keeping her urine sugar-free although she was on a diet-containing upwards of 2,300 calories. The patient was then being fed liberally of fat, which probably was a serious mistake. During the whole year 1916 great difficulty was experienced in keeping her urine sugar-free for any length of time. Frequent rest days were necessary for that purpose. The first blood sugar determination was made March 10, 1916, and was 0.17 per cent. Routine blood sugar examinations were not begun until September, 1917. It is quite probable, however, that the patient had a high level all of the time, for traces of sugar were frequently appearing in the urine, indicating that the food intake kept the blood sugar level up to the point of the threshold. The data shown in the chart is taken at random from the patient's record and is characteristic of the course of her metabolism. As in the other severe cases shown in this study, it was quite impossible to reduce the blood sugar level to anything approximating normal by fasting or underfeeding. Until a few days before death, which was induced by a severe cold, there was no appreciable evidence of acidosis.

Chart 6.—Case 2218. Mild diabetes associated with advanced arteriosclerosis and chronic interstitial nephritis. The kidney lesion in this case was much more serious than the diabetes and it is not improbable that the high blood sugar curve is thus explained.

Chart 7.—Case 2184. This patient has had diabetes for more than eight years. One month before admission to the hospital a perforating ulcer developed on one foot. In a short time this foot had become gangrenous so that on November 22 it was thought wise to amputate the leg below the knee. The wound healed slowly, several gangrenous sloughs developing, so that during the entire hospital stay the wound remained open and infected, although gradually improving. Ultimately it healed and the patient made a good recovery so that he is sugar-free on a liberal diet. The persistent high blood sugar in this case is undoubtedly induced by the gangrene.

Chart 8.—Case 2122. This patient was admitted to the hospital with severe moist gangrene of one foot. Her failure of metabolism became more and more pronounced, acidosis becoming increasingly severe each day up to the time of death, Oct. 22, 1917. Attention is called to the persistent high blood sugar curve in this case, in spite of the low diet. We have studied several cases of this type and have observed that the blood sugar curve remains high in the presence of severe infection and gangrene.

Chart 9.—Case 1680. This young woman had severe diabetes for about two and one-half years before she finally succumbed. During that time she was in the hospital for observation several times, staying several weeks each time. She was unusually faithful and closely cooperated in the study. This patient had a high degree of cholesterinemia, but up to a short time before death there was an absence of acidosis notwithstanding the low diet. It was quite impossible to get her blood sugar down to the normal limits, even with the most rigorous treatment. Weeks of total abstinence from carbohydrates, even excluding thrice cooked vegetables, did not suffice. The dextrose nitrogen ratio at the time of the last observation was 5.11. This patient well illustrates the point that cases presenting intractably high blood sugars have an ominous prognosis.

Chart 10.—Case 2115. This young woman had severe diabetes for about two years before coming under observation. When admitted to the hospital she presented the usual clinical evidences of severe diabetes. It was quite

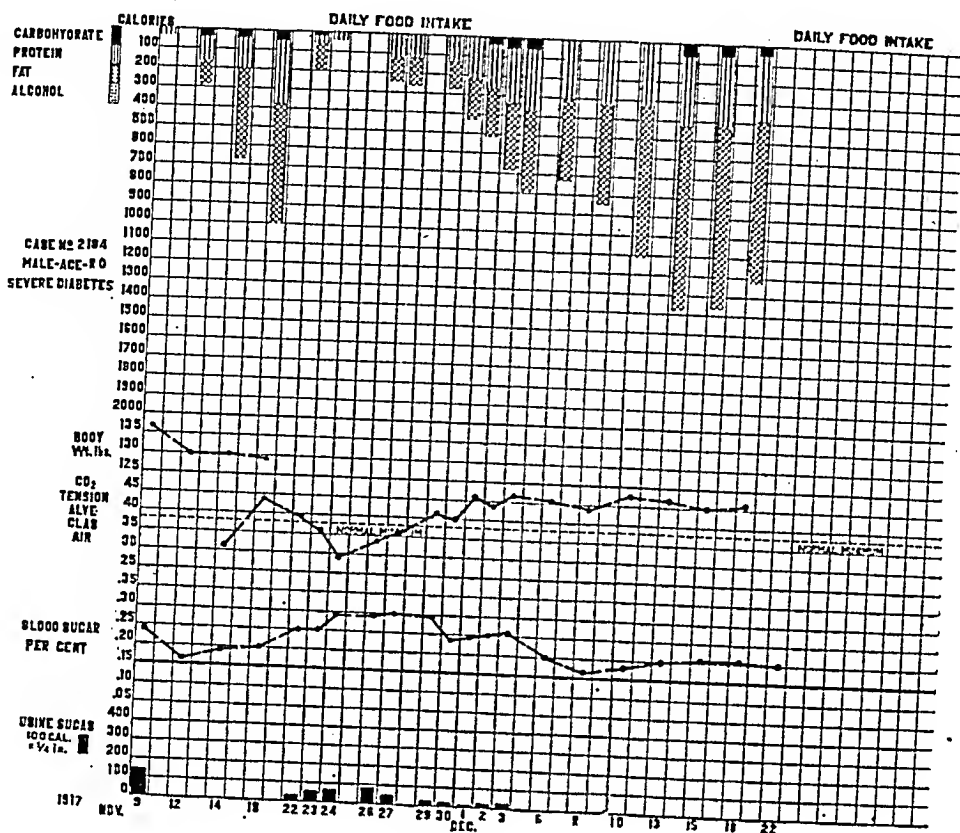


Chart 7

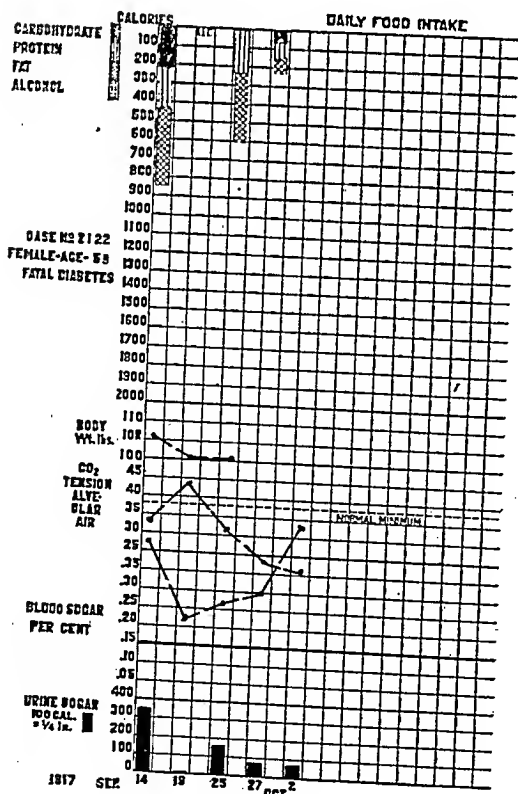


Chart 8

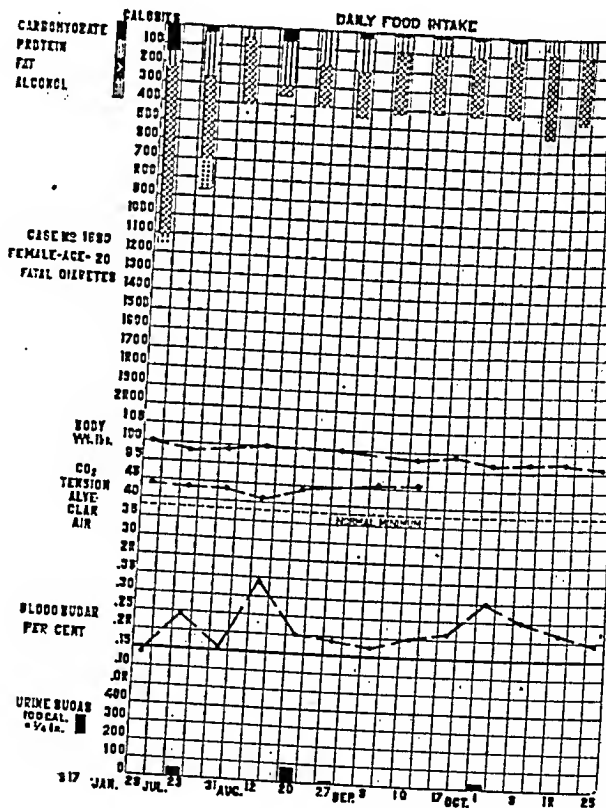


Chart 9

impossible, even on very low diets, to reduce her blood sugar level to normal limits. She was accordingly a very discouraging case for treatment. The very high blood sugar levels and large urinary sugar outgo at the end are probably explained by the fact that the patient ate surreptitiously other food than the prescribed diet.

Chart 11.—Case 2127. This case is of interest and importance to the student of diabetes because it illustrates the serious difficulties which are occasionally encountered in attempting to control the disease. The patient was an intelligent, cheerful young woman who cooperated most carefully in this

blood sugar to normal. Beginning Jan. 15, 1916, and for five days, the patient was given absolutely no food. This reduced the blood sugar to 0.13 per cent. For the next five days less than 500 calories of food per day were allowed, yet the blood sugar went up to 0.17 per cent. Thereafter, for the next six months, the diet was rarely permitted to get above 800 calories, often it was much below this, yet in spite of this continued and prolonged underfeeding, the blood sugar maintained a high level, ranging from 0.20 to 0.40 per cent. It will be observed that the point where sugar appeared in the urine or the renal threshold, was well above 0.20 per cent. from the beginning.

It is the experience of the writers that when a patient presents such a persistent and unyielding blood sugar curve as is exhibited by this case, the prognosis is very bad and the termination of the disease in death close at hand.

Chart 12.—Case 2253. Diabetes was first discovered in this patient Jan. 1, 1917. One year later a small hard mass of granulation tissue formed under the nail of the right great toe. From this, there oozed a thin, watery discharge. At the time the patient came under the observation of the writers, Jan. 23, 1918, she was not in good condition, having just undergone a month's fasting and underfeeding in another hospital. She was then fasted, kept on a carbohydrate-free diet and underfed for two weeks without appreciable effect on her blood sugar level. The granulomatous mass was removed, Feb. 6, 1918, by Dr. W. I. Dean. Following the operation there was immediate decline in the blood sugar level and with it an increase in food tolerance and note-

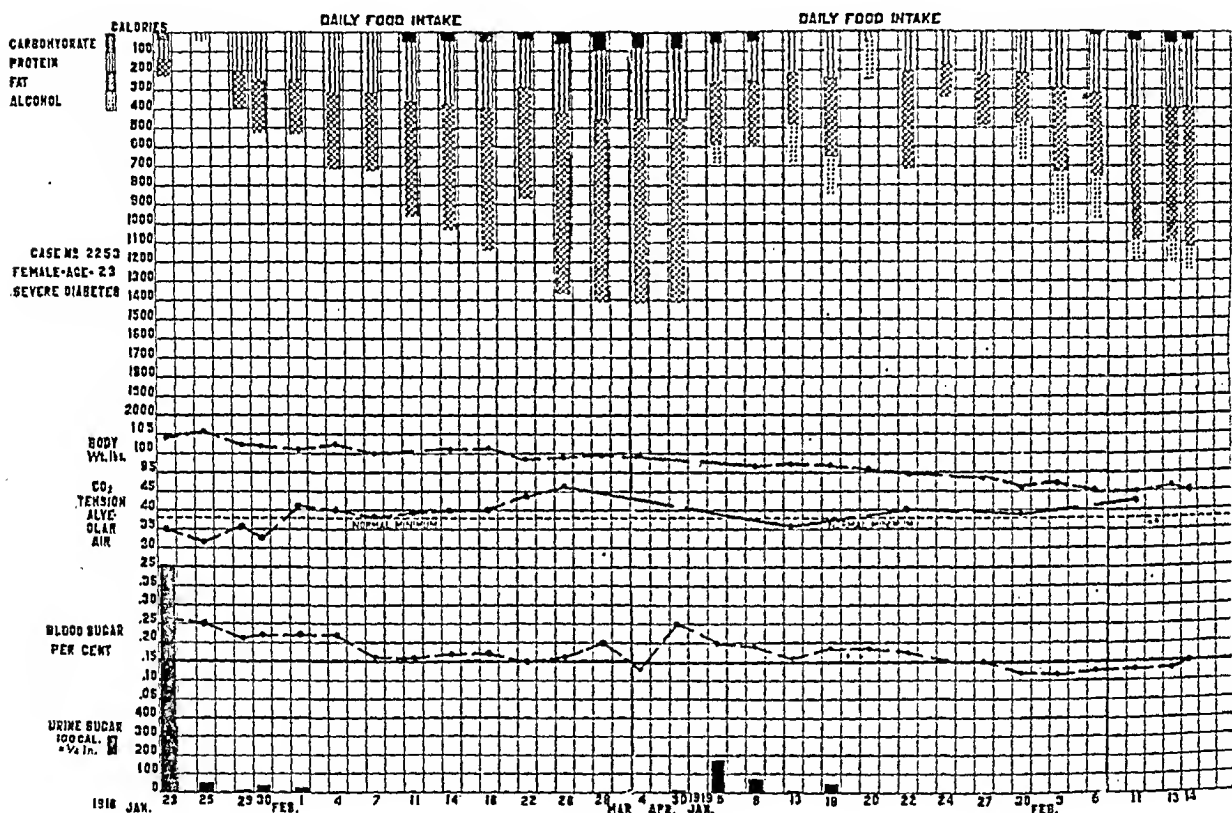


Chart 12

worthy clinical improvement. The patient left the hospital March 4, 1918, on a diet that was probably a little too high. She did very well for several months and then became careless in eating. She returned to the hospital, Jan. 5, 1919, with a blood sugar of 0.20 per cent. She was then kept on a very low carbohydrate-free diet, averaging less than 600 calories, for nearly a month. During this time there was a gradual decline in the blood sugar level to approximately 0.12 per cent and a material clinical improvement. It will be noted that alcohol has been used in this case. From observations on a number of intractable cases of diabetes with high blood sugar, the writers are inclined to the view that small quantities of alcohol are of value in promoting carbohydrate metabolism.

This case illustrates the serious influence of sores and ulcers on the metabolism of diabetics and also the persistence and care which must be exercised in restoring the blood sugar to normal.

CONCLUSIONS

1. It is important to distinguish between blood sugar level and the renal threshold for sugar. The height of the blood sugar level at which appreciable quantities of sugar are eliminated in the urine is considered the renal threshold. The blood sugar level in various stages of diabetes may be much higher or lower than this point.

2. There is no striking relation between the height of the renal threshold and the duration of the diabetes. It would appear, however, from the analysis of our sixty-five cases that the threshold tends to rise with the increasing duration of the disease.

3. Younger diabetics as a rule have low or normal thresholds. The threshold rises with advancing years.

4. When the diabetes is mild or quiescent, the point at which the kidneys eliminate sugar is stationary; but when the disease becomes progressive, the threshold tends to rise. Indeed, before death the blood sugar renal threshold may reach great heights with little or no sugar appearing in the urine.

5. A rising renal threshold for sugar in the face of careful dietary treatment is a serious prognostic sign.

6. A high renal threshold for sugar in mild diabetes under proper dietary regulations usually indicates some complication, as arterial hypertension.

7. A high renal threshold for sugar may mean a physiologic expedient to conserve food material.

8. Our experience leads us to the belief that persistent high blood sugar levels promote exhaustion and rapid decline of function, and the high threshold is merely a safety measure.

9. In severe diabetes, where extremely low diets are necessary to maintain life, the high threshold is essential to take care of the seriously impaired carbohydrate metabolism.

10. In the treatment of diabetes it is desirable to maintain the blood sugar level as nearly normal as possible, even though severe restrictions in diet may be necessary for this purpose, notwithstanding the fact that the high threshold will permit of a much more liberal diet without the appearance of sugar in the urine.

11. We regard with misgiving and apprehension any plan of treatment of diabetes which permits of food just short of the point of glycosuria. In short, we believe that diabetes should be controlled on the basis of the blood sugar level rather than by urine tests.

12. A persistent low blood sugar level may be regarded as an extremely favorable prognostic sign.

13. A persistent high blood sugar level, in spite of undernutrition, usually points to an unfavorable outcome.

14. In our experience, cases which hitherto had been intractable and had shown progressive loss of food tolerance, when the blood sugar level was disregarded, have been greatly benefited and their tolerance increased by regulating the food intake so as to insure, when possible, a normal blood sugar level.

15. While we regard 0.15 per cent. as the maximum normal digestion blood sugar level, we believe patients are safer when this level is not higher than 0.13 per cent.

388 Monroe Avenue.

OBSERVATIONS ON TOLERANCE AND RATE OF UTILIZATION OF GLUCOSE IN A SERIES OF INDIVIDUALS EXHIBITING VARIOUS DEGREES OF DIABETES MELLITUS

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WITH THE COLLABORATION OF
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Third Paper

Hamman and Janney have both recently reviewed the literature on this phase of the problem; accordingly, we shall only comment on some of the more important investigations. Hopkins¹ points out that in health a moderate rise up to 0.14 or 0.15 per cent. in blood sugar follows the ingestion of 100 gm. of glucose. The curve reaches its peak in from one half to two hours, then quickly subsides. In disturbed carbohydrate metabolism, a normal sugar concentration may be associated with a most pronounced alimentary hyperglycemia. In diabetes, the hyperglycemia is very pronounced; the peak is reached in from one half to three hours and is prolonged.

According to Taylor and Hutton² in the majority of healthy males there is no limit to the assimilation of glucose. Glycosuria does not follow the largest possible ingestion of glucose.

Wilder and Sansum³ in an elaborate study of the subject raise serious objection to the oral method of glucose administration on the ground that it introduces the questionable factor of absorption. In their studies they made use of the method of continuous intravenous injection at accurately controlled rates devised by Woodyatt, Sansum, and Wilder.⁴ They conclude that when sugar appears in the urine, as evidenced by a reduction in Haines' solution, the limit of tolerance is reached. Glycosuria is produced in normals when the rate of injection lies between 0.8 and 0.9 gm. of glucose per kilogram of body weight per hour. Nondiabetic pancreatic disease may evince a lowered tolerance even when alimentary tests show no change.

On the basis of our own experience, the fundamental objection to the work of these investigators is that they do not give weight to the blood sugar levels, which is of primary importance in diabetes.

1. Hopkins, A. H.: *Am. J. M. Sc.* **149**:254, 1915.

2. Taylor, A. E., and Hutton, F.: *J. Biol. Chem.* **25**:173, 1916.

3. Wilder, R. M., and Sansum, W. D.: *Arch. Int. Med.* **19**:311, 1917.

4. Woodyatt, R. T., Sansum, W. D., and Wilder, R. M.: *J. A. M. A.* **65**:2067, 1915.

Nor do they establish the blood sugar threshold of the kidneys, but merely the rate of injection and amount of glucose which can be introduced into the body up to the point of glycosuria. Janney and Isaacson⁵ have made similar objection.

In our studies we used the method suggested by Hamman and Hirschman,⁶ with whose conclusions our investigations are in substantial agreement. Janney and Isaacson have recently published an account of the blood sugar test used at the Montefiore Home and Hospital, New York City. In their method, in the administration of the glucose and water, they take into consideration the weight of the individual: 1.75 gm. of sugar are given for each kilogram of body weight. For each gram of glucose, 2.5 c.c. of water are used. We think this procedure an advantage and shall incorporate it in our future study, although it will be seen from an examination of our curves that the relation of the amount of sugar to the weight of the patient is not so important as to vitiate investigations made in the manner suggested by Hamman and Hirschman.⁶

It is the practice of many investigators in this field to make hourly observations on the blood sugar level. We prefer the half-hourly interval proposed by Hamman and Hirschman⁶ for the reason that in seven out of eleven nondiabetics the maximum blood sugar level was reached one half hour after the ingestion of the glucose, and at the end of one hour the level in these cases had subsided appreciably.

The method as used by us was as follows: Samples of blood and urine are obtained from the fasting patient in the morning. Immediately after, he is given orally 100 gm. of glucose dissolved in water, to which is added the juice of one orange. This is then shaken up with cracked ice and made up to approximately 300 c.c. of fluid; 200 c.c. of water are administered one half and one hour later, at which points further blood and urine specimens are secured, additional and final specimens being secured two hours from the beginning of the test.

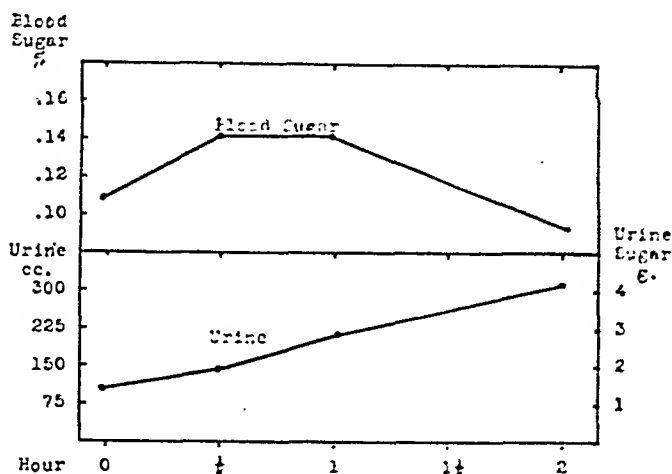
GLUCOSE UTILIZATION TESTS IN A GROUP OF NONDIABETICS

The following patients from time to time have passed urine containing a reducing substance which has been thought to be sugar. Some of them have undergone treatment for diabetes. The glucose utilization test employed by us is the one suggested by Hamman and Hirschman.⁶ The data are plotted in the accompanying curves. Urine sugar is shown in vertical hatching. Urine volume and blood sugar are plainly indicated in the diagrams. A note of explanation and interpretation follows each curve.

5. Janney, N. W., and Isaacson, V. I.: *J. A. M. A.* **70**:1131, 1918.

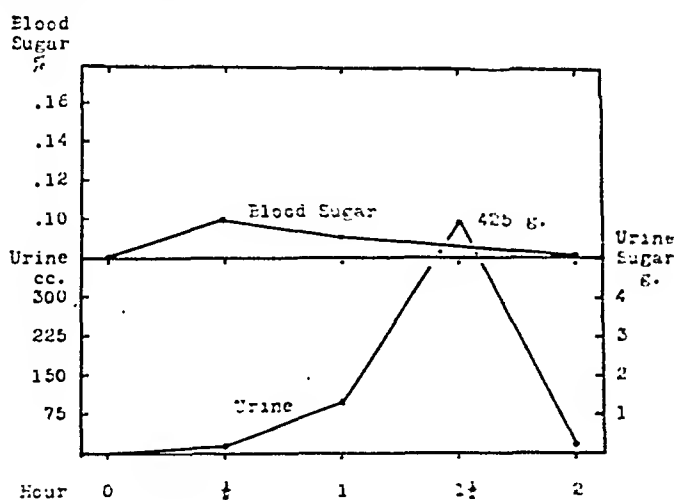
6. Hamman, L., and Hirschman, I.: *Arch. Int. Med.* **20**:761, 1917.

Chart 1.—Case 1620. Glucose utilization test in a nondiabetic woman aged 34. Body weight, 117 pounds. Hyperthyroidism.



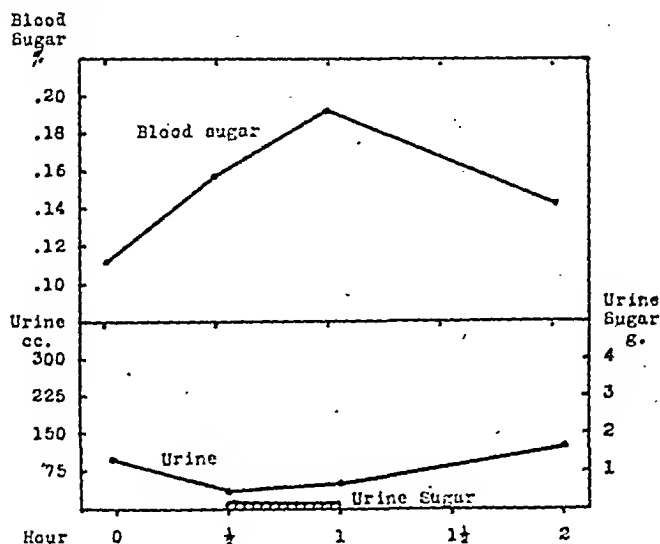
COMMENT.—Attention is called to the slight but appreciable rise in blood sugar in the first half hour. This curve indicates a normal utilization. There was no urine sugar.

Chart 2.—Case 2354. Glucose utilization test in a nondiabetic woman aged 31. Body weight, 114 pounds.



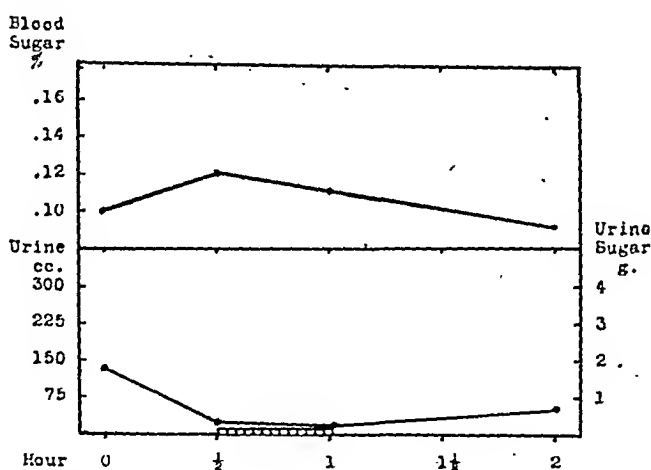
COMMENT.—Sugar is alleged to have been found in the urine of this patient by an irregular practitioner. There is a history of frequent and copious urination; also serious mouth infection. Eleven teeth are crowned and practically all show apical abscesses. There is a slight involvement of the thyroid. The blood sugar curve is below normal.

Chart 3.—Case 2205. Glucose utilization test in a man aged 24. Epilepsy. Body weight, 125 pounds.



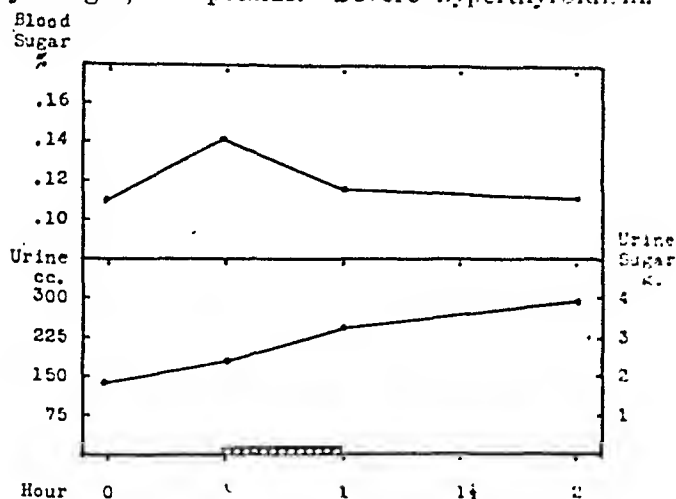
COMMENT.—The patient has been a victim of epilepsy since 7 months old. His normal blood sugar is approximately 0.11 per cent. (average of four tests). The utilization test was made, then the patient was given 3 grains of anterior pituitary gland daily for three days and the glucose utilization test repeated. The results of each test were strikingly similar. This curve, which is higher than normal, suggests some disturbance in metabolism which may be general in character. The blood uric acid was 5 mg. per 100 c.c., urea 50 mg. per 100 c.c. (average of two tests), cholesterol 187 mg. per 100 c.c.; general nutrition poor.

Chart 4.—Case 2208. Glucose utilization test in a nondiabetic man, aged 54. Body weight, 118 pounds. Mild chronic diffuse nephritis.



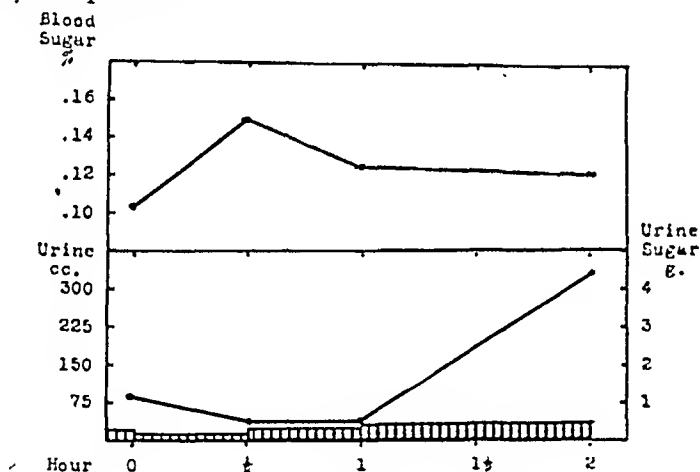
COMMENT.—When this patient was admitted to the hospital one month previous to this examination and while on a moderately restricted carbohydrate diet, three blood sugar determinations were as follows: 0.17, 0.14, 0.15 per cent. Several blood ureas with patient on a low protein diet ranged from 50 to 89 mg. per 100 c.c. blood.

Chart 5.—Case 2224. Glucose utilization test in a nondiabetic woman aged 22. Body weight, 102 pounds. Severe hyperthyroidism.



COMMENT.—Attention is called to the slight rise in blood sugar in the first half hour. A trace of sugar appeared in the hour urine sample. This curve is essentially normal.

Chart 6.—Case 1352. Glucose utilization test in a nondiabetic man aged 23. Body weight, 150 pounds.



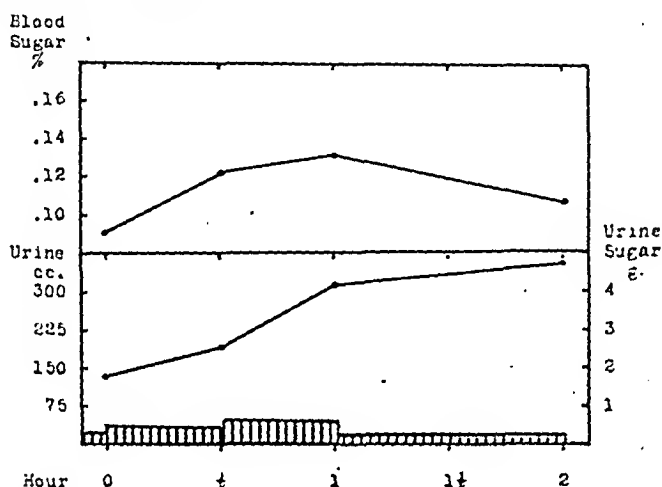
COMMENT.—This patient was rejected for life insurance because sugar was alleged to have been found in the urine. A reducing substance was found in the urine which was levorotatory. Its identity was not clearly established because of lack of necessary reagents. Obviously it was not glucose. The graph shows that it was present in the urine in small amounts with the blood sugar 0.10 per cent. and that the blood sugar curve was not abnormally influenced by the oral administration of the 100 gm. of glucose.

GLUCOSE UTILIZATION TESTS IN A SERIES OF SUPPOSED DIABETICS

We have studied, after the plan of Hamman and Hirschman,² five patients in whom there has been a history of probable glycosuria. All of these patients have from time to time been treated for diabetes mellitus for the reason that copper reducing substances have been found in the urine. None gives a typical blood sugar curve observed in true diabetes; in fact, the curves do not differ from those observed in normals. In Cases 2232 and 2394, the figures given as urinary sugar are based on reduction tests using Benedict's quantitative solu-

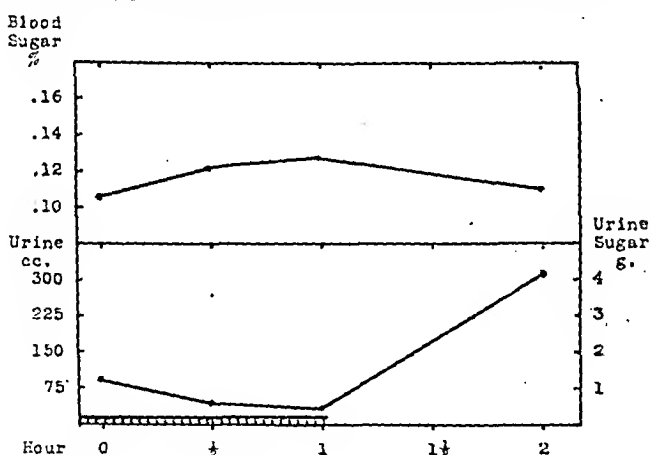
tion. We later studied the reducing substance passed by these two patients and established that it is not glucose but probably some conjugate of glycuronic acid. Inability to secure the necessary reagents prevents the definite recognition of these substances. Some cases of the character shown in this group are undoubtedly renal diabetes, of which Case 2228 is an example.

Chart 7.—Case 2228. Glucose utilization test in a man aged 44. Probably renal diabetes. Body weight, 132 pounds.



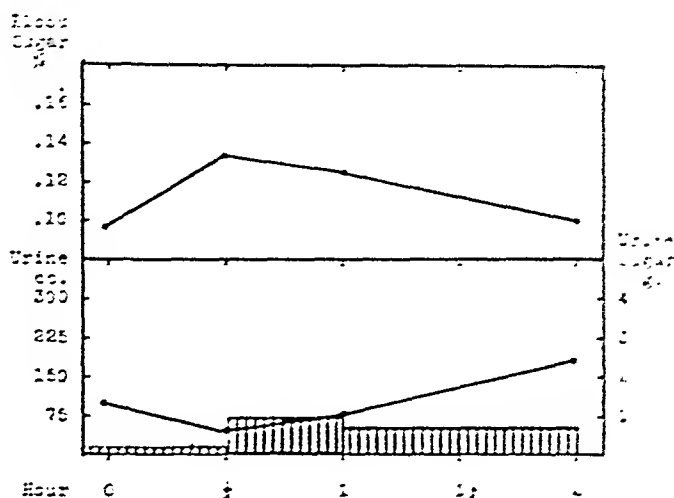
COMMENT.—This patient complains only of loss of weight. Small amounts of sugar have been found in the urine with the patient on a general diet. At the beginning of the test a trace of sugar was found in the urine, with blood sugar at 0.09 per cent., indicating a low threshold. The blood sugar curve is normal, indicating satisfactory utilization of glucose.

Chart 8.—Case 2232. Glucose utilization test in a boy aged 14. Body weight, 94 pounds. Supposed diabetic, but probably normal.



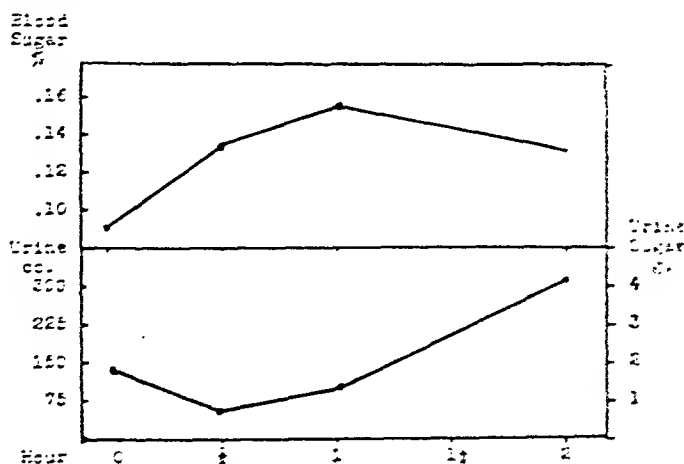
COMMENT.—This boy has passed in his urine from time to time for the past three years copper reducing substances. This has led to the assumption that he has diabetes; accordingly he has undergone sporadic dietary treatment. The copper reducing substance in the urine is levorotatory, does not form the characteristic crystals with phenylhydrazin, and is probably a conjugate of glycuronic acid. The utilization of glucose in this case is normal. The test was of distinct value in determining whether or not the patient had a failure of carbohydrate metabolism.

Chart 9.—Case 2394. Glucose utilization test in a man aged 67. Probable renal diabetes. Body weight, 143 pounds.



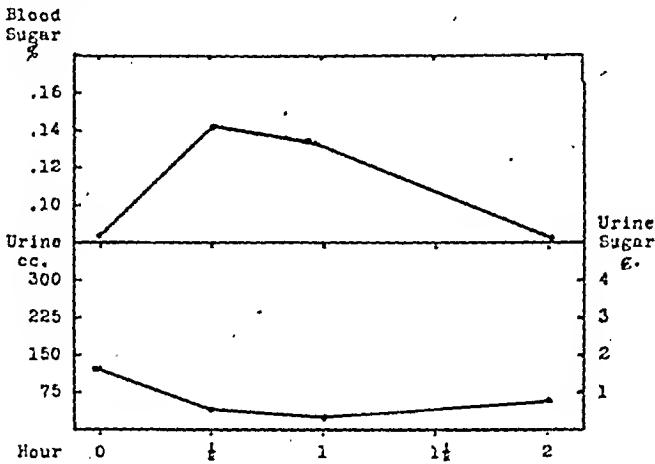
COMMENT.—This patient has passed copper reducing substances in urine for five years, during which time he has been subjected to diabetic dietary and other treatment. Even on a general diet, the reducing substance is never present except in small amounts, is levorotatory, and does not form characteristic glucosazone crystals with phenylhydrazin. Digestion blood sugar ranges normally from 0.09 to 0.13 per cent. The usual clinical symptoms of diabetes have been absent. During the above utilization test the patient did pass appreciable amounts of glucose with blood sugar levels below 0.10 per cent.; accordingly this case might be interpreted as one showing at times the phenomena of renal diabetes.

Chart 10.—Case 2283. Glucose utilization test in a nondiabetic woman aged 20. Body weight, 122 pounds.



COMMENT.—A reducing substance thought to have been sugar was first found in this patient's urine in 1912. Since then the patient has had sporadic dietary treatment for diabetes. There is a history of epigastric distress, tenderness over the gallbladder, belching of gas, etc., suggesting a mild cholecystitis with possible pancreatic involvement. In our experience, such cases frequently show a slight glycosuria. The curves in chart 10 are practically normal.

Chart 11.—Case 2303. Glucose utilization test in a nondiabetic man aged 37. Body weight, 162 pounds.

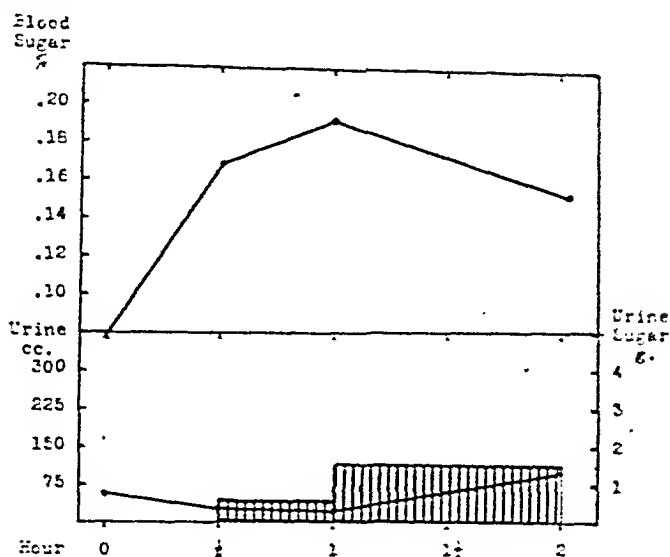


COMMENT.—A copper reducing substance has been found in this patient's urine on several occasions by his family physician. There is nothing in his clinical history to suggest diabetes. It is quite evident that he is able to utilize the large amount of glucose in this test in a normal manner.

GLUCOSE UTILIZATION TESTS IN A GROUP OF VERY MILD OR DOUBTFUL DIABETICS

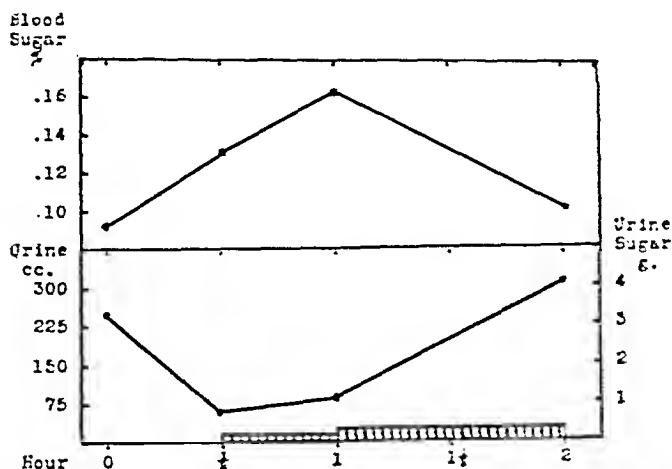
The following patients have shown from time to time traces of reducing substance in the urine. The absence of symptoms and the variability of the findings have given rise to doubt in the minds of many of the physicians who have examined these patients as to whether or not they have true diabetes. The rather high blood sugar within the half hour after the ingestion of the sugar, together with its persistence for an hour or so, the appearance of increased urine sugar, and the diuresis, all, in a very mild degree, point to the early stage of diabetes.

Chart 12.—Case 1594. Glucose utilization test in a man aged 41. Very mild diabetes. Body weight, 150 pounds.



COMMENT.—There is a complete absence of diabetic symptoms in this case. Sugar was first discovered in the urine in the course of a casual examination, and since has been found only occasionally although the patient lives on a very liberal diet. The prompt rise in the blood sugar curve, its persistence at a higher level than normal, together with the glycosuria, suggest a mild diabetes.

Chart 13.—Case 1716. Glucose utilization test in a man aged 47. Very mild diabetes. Body weight, 200 pounds.



COMMENT.—In this case also there is a complete absence of symptoms of diabetes. The patient lives on an unrestricted diet, with only an occasional trace of sugar in the urine. The curves suggest a very mild, indeed, a doubtful diabetes.

Chart 14.—Case 2230. Glucose utilization tests in a man aged 23. Very mild diabetes. Low grade tuberculosis. Body weight, 140 pounds. Curve A.

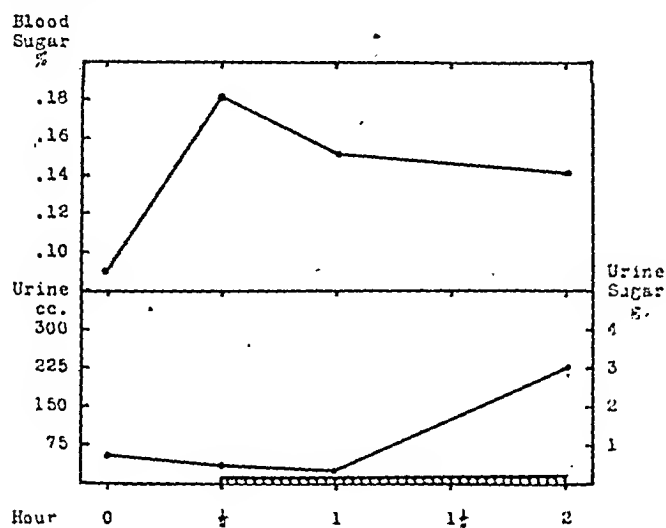
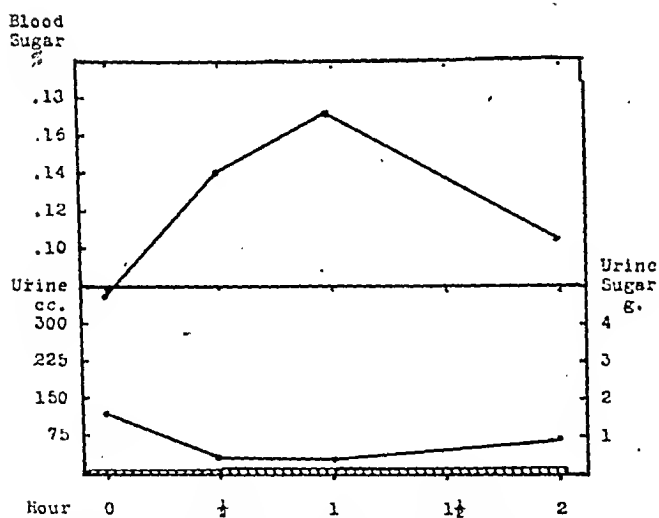
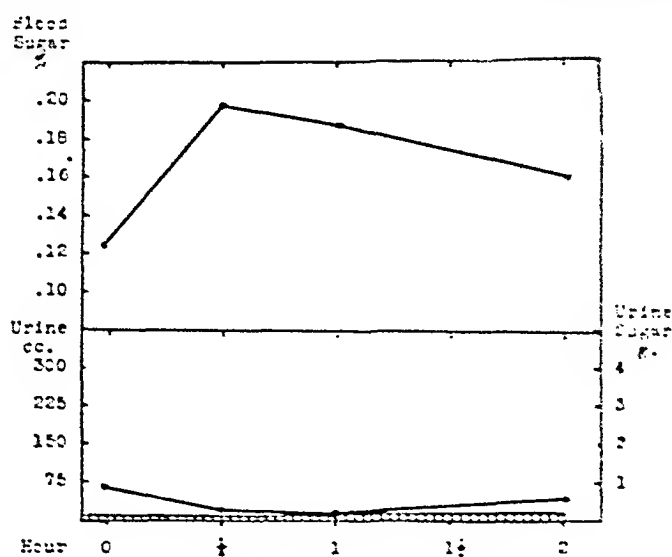


Chart 15.—Case 2230. Curve B.



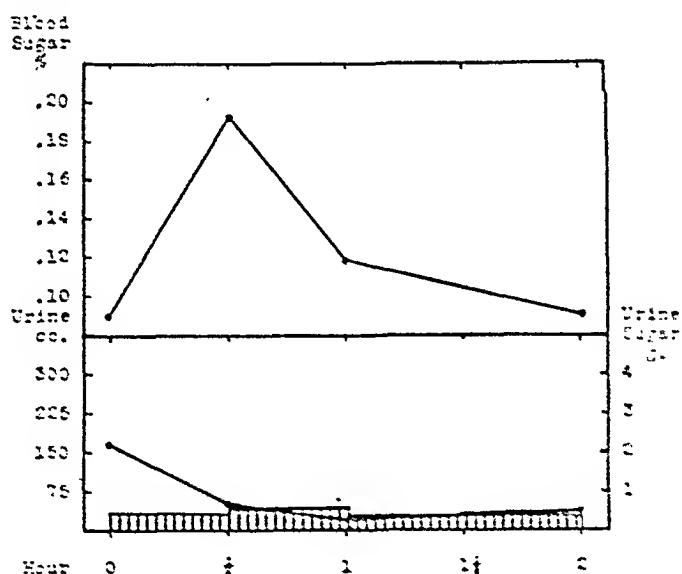
COMMENT.—This patient exhibits none of the clinical symptoms of diabetes. Sugar was found in the urine in the course of a routine examination in the Monroe County Tuberculosis Sanatorium. The examination shown in curve B was made approximately five months later than that shown in A. They coincide fairly well and suggest, as do the other curves in this group, a very mild diabetes.

Chart 16.—Case 2217. Glucose utilization test in a woman aged 50. Cardiac hypertension. Mild diabetes. Body weight, 135 pounds.



COMMENT.—This patient exhibits none of the clinical symptoms of diabetes. Traces of sugar are frequently found in the urine. The blood sugar curve in this test, as in the preceding cases, points to a very mild diabetes.

Chart 17.—Case 1948. Glucose utilization test in a man aged 38. Very mild diabetes. Body weight, 148 pounds.

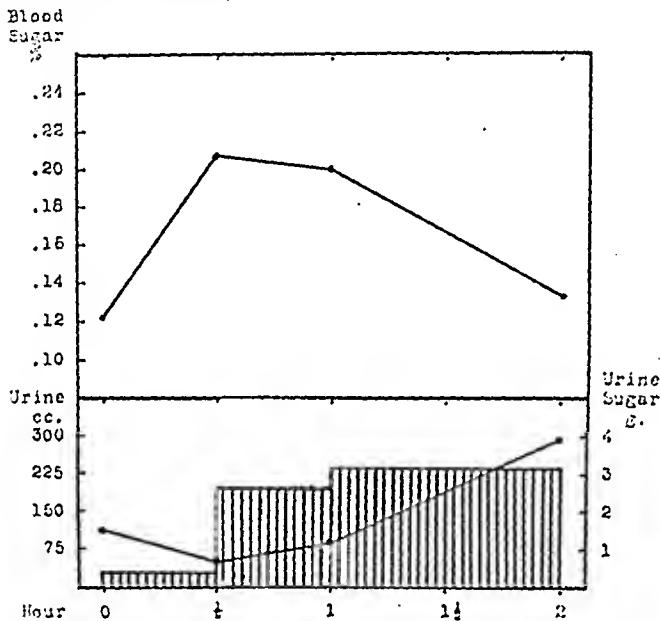


COMMENT.—This patient complained only of loss of weight. Even on the most generous diets this patient shows sugar in the urine only occasionally. His digestion blood sugar level is usually about 0.11 per cent., and has never been found higher than 0.14 per cent. The sharp rise of the blood sugar curve in this test with the glycosuria suggests a slightly diminished carbohydrate metabolism.

GLUCOSE UTILIZATION TESTS IN A SERIES OF CASES OF MILD BUT
DEFINITE DIABETES

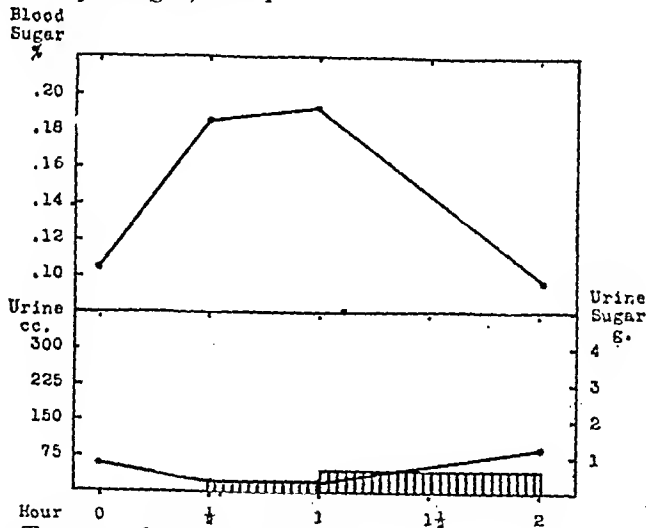
In the following group are those patients who showed definite clinical symptoms of diabetes, as loss of weight, polyuria, thirst, etc. They are very mild in character, however, and very amenable to treatment. This group is typical of a large number of patients who pay no attention to their diabetes and suffer very little from its discomforts.

Chart 18.—Case 2404. Glucose utilization test in a man aged 34. Mild diabetes of five months' standing.



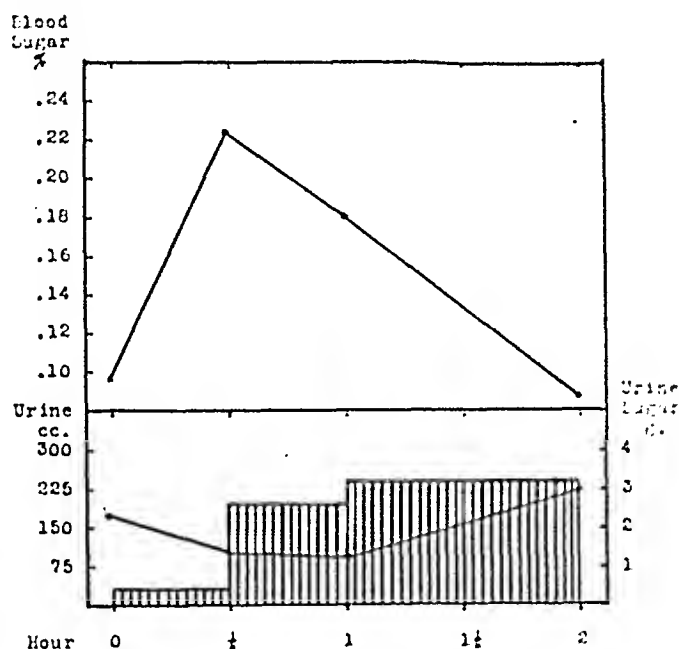
COMMENT.—This patient complained only of weakness. Sugar found in the urine in small amounts frequently but not constantly. The blood sugar curve shows an undoubted failure in sugar metabolism.

Chart 19.—Case 1000. Glucose utilization test in a man aged 26. Very mild diabetes. Body weight, 128 pounds.



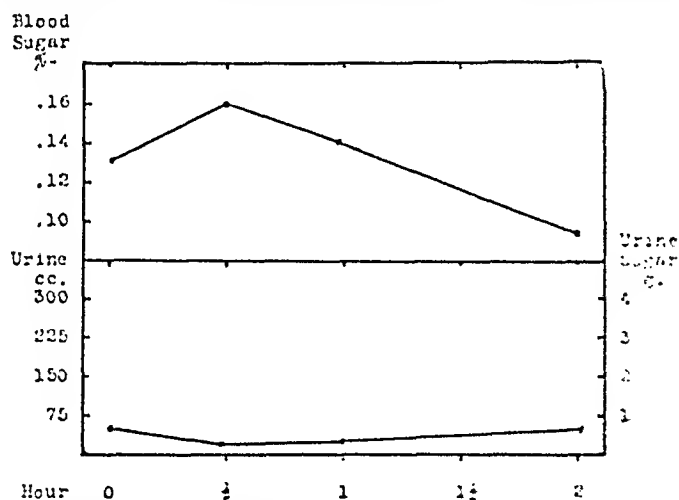
COMMENT.—Traces of sugar occasionally appeared in the urine of this patient at irregular intervals and while on a general diet. The blood sugar curve dropped to normal at the end of two hours, suggesting but little impairment in the power of utilization.

Chart 20.—Case 2435. Glucose utilization test in a man aged 34. Very mild diabetes. Body weight, 114 pounds.



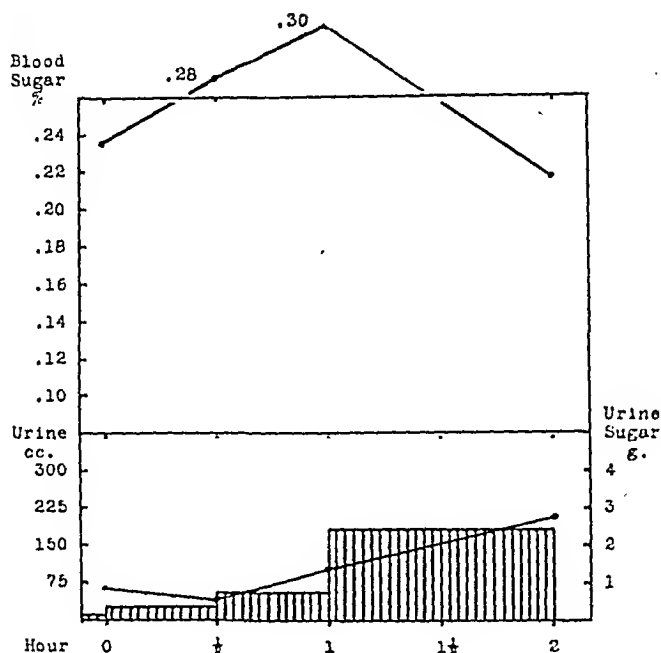
COMMENT.—This patient gave a history of considerable loss of weight and weakness extending over a period of four years. There was an absence of thirst and polyuria. Sugar was present in his urine only occasionally even on a heavy diet. The low initial blood sugar and the prompt return to normal two hours after the ingestion of the sugar point to the slight failure in ability of the body to utilize glucose, while the sharp rise in the curve together with the glycosuria are evidences of abnormal metabolism.

Chart 21.—Case 2140. Glucose utilization test in a man aged 38. Diabetes of one year's standing. Body weight, 210 pounds. Apparent recovery.



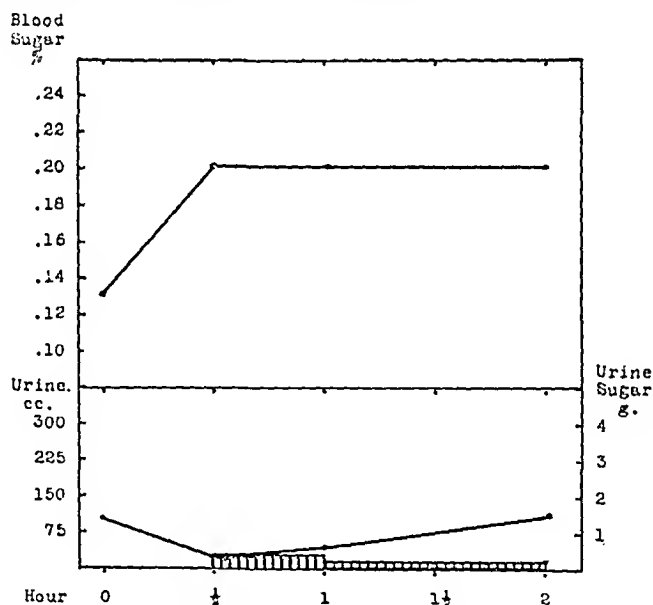
COMMENT.—Patient is a physician. One year before, on a moderately restricted diet, patient excreted urine of a specific gravity 1.045; urine sugar 3.8 per cent., blood sugar 0.25 per cent. Several subsequent examinations of blood sugar were from 0.20 down to 0.11 per cent. during the course of treatment. For several months patient has been following a general diet, with no restrictions except as to amount of cane sugar, which is eaten sparingly. This test suggests a normal utilization of glucose.

Chart 22.—Case 2348. Glucose utilization test in a man aged 35. Mild diabetes of three months' standing. Body weight, 186 pounds.



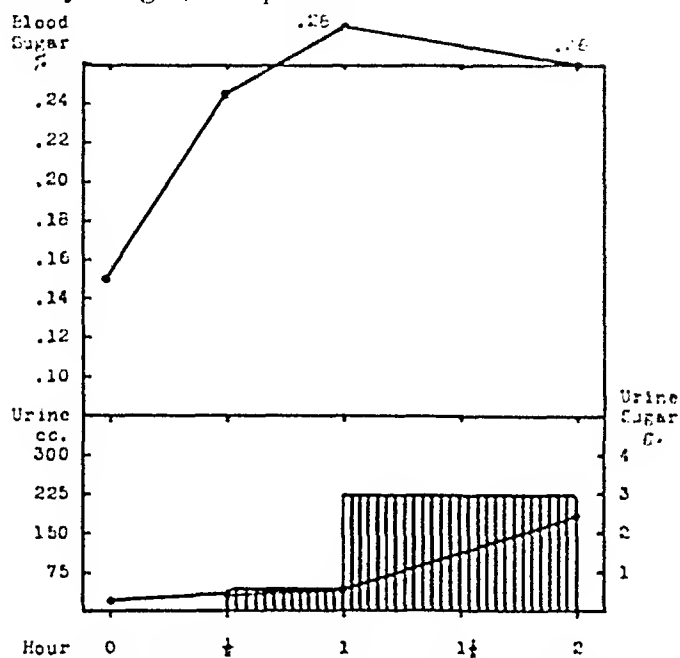
COMMENT.—This patient exhibited very slight but definite clinical evidence of diabetes. This is shown unmistakably in the blood sugar curve. He yielded promptly to treatment and was able to return to a diet which, aside from its cane sugar content, was fairly normal.

Chart 23.—Case 2324. Glucose utilization test in a man aged 61. Mild diabetes of four years' standing. Body weight, 173 pounds.



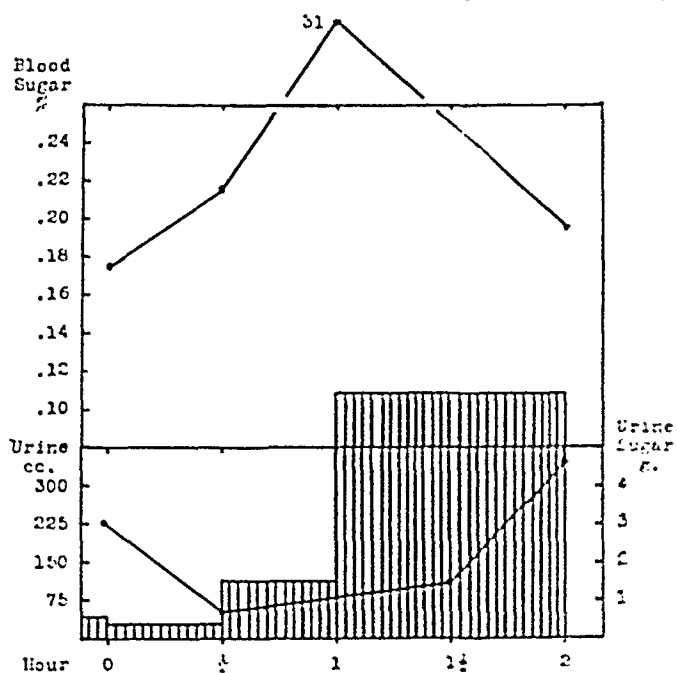
COMMENT.—There was an absence of the usual clinical symptoms of diabetes in this case, pointing to the mildness of the disease. The blood sugar curve shows a pronounced rise and maintains a persistently high level, which, with the glycosuria, points to defective glucose utilization.

Chart 24.—Case 2476. Glucose utilization test in a man aged 70. Mild diabetes of two years' standing associated with chronic cholecystitis and pancreatitis. Body weight, 130 pounds.



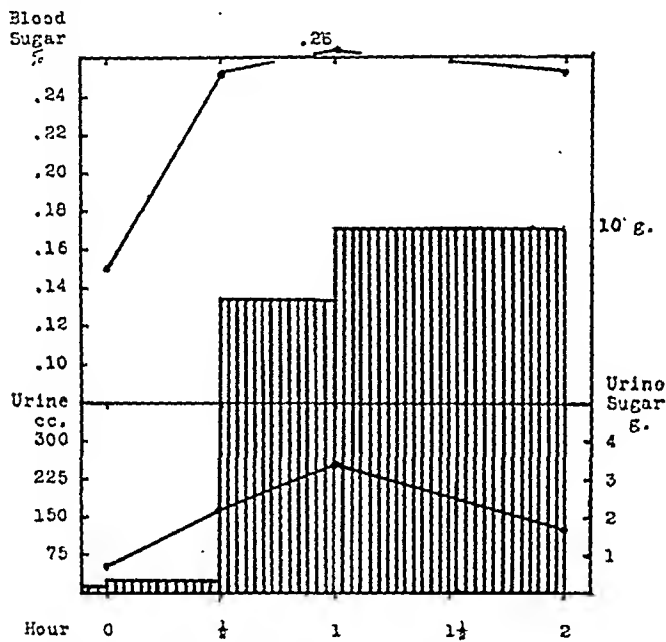
COMMENT.—Patient had had symptoms of cholecystitis for more than ten years. He has had none of the clinical symptoms of diabetes except that on a generous diet he excretes small amounts of sugar in the urine. In the experience of the writers, the diabetes associated with cholecystitis is usually of the mild character exhibited by this patient.

Chart 25.—Case 2338. Glucose utilization test in a man aged 61. Mild diabetes of about three months' standing. Body weight, 200 pounds.



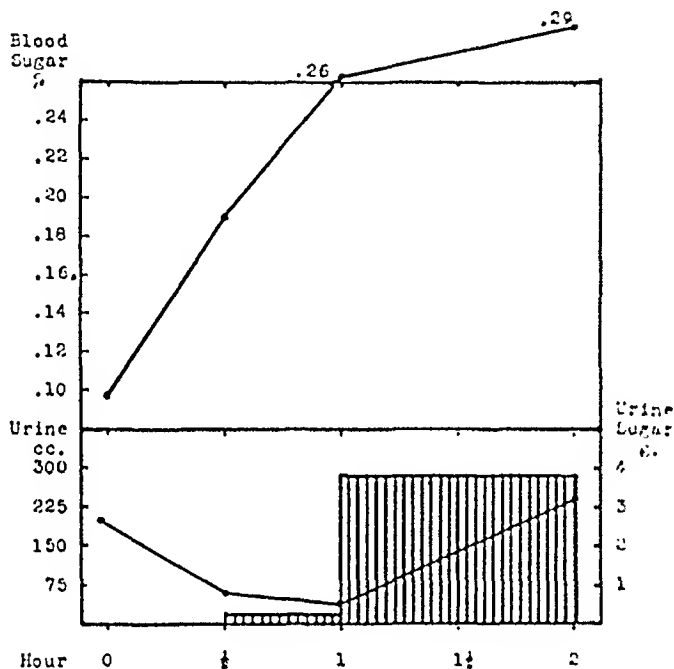
COMMENT.—This patient exhibited but very slight clinical evidence of diabetes in a gradual loss of weight. On a liberal diet in which cane sugar is eliminated and foods containing high percentages of starch are limited, he maintains a digestion blood sugar level of from 0.09 to 0.14 per cent. He must, therefore, be classed as a mild diabetic. The graph in this case shows a definite failure in sugar utilization.

Chart 26.—Case 2289. Glucose utilization test in a woman aged 58. Mild diabetes of five months' standing. Body weight, 150 pounds.



COMMENT.—This patient had none of the clinical symptoms of diabetes except a slight eczema of the vulva. Her urine, even on a very liberal diet, showed small amounts of sugar inconstantly. Her digestion blood sugar level on slightly restricted diets ranges from 0.09 to 0.15 per cent.; hence it will be seen that she has a mild diabetes. The graph of the utilization test, however, points clearly to a definite failure in carbohydrate metabolism.

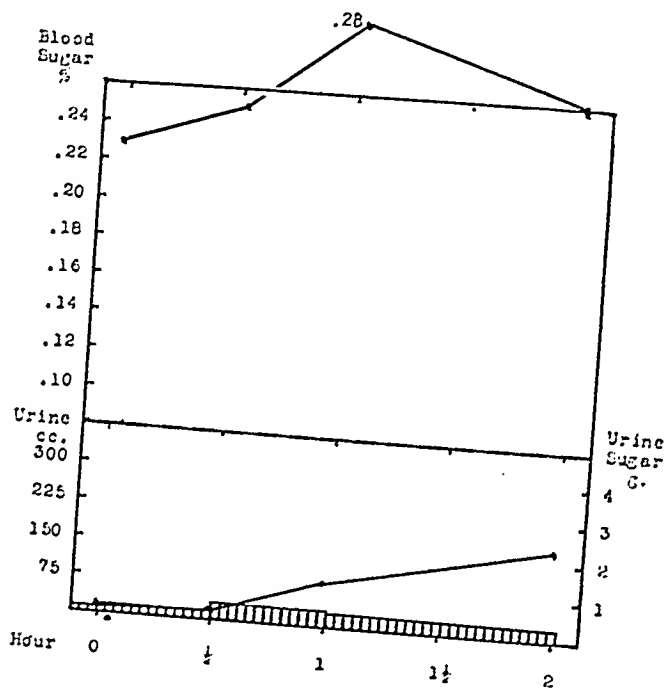
Chart 27.—Case 2309. Glucose utilization test in a woman aged 51. Mild diabetes and cardiac hypertension. Illness dates over a period of four years. Body weight, 148 pounds.



COMMENT.—There were no clinical symptoms of diabetes in this case; all of the evidence of illness present seemed related to the rather serious high arterial pressure. The patient's blood sugar on a rather liberal diabetic diet, 120 gm. of carbohydrate, 1,900 calories, ranged from 0.10 to 0.12 per cent. It is possible that this patient has not diabetes but that the striking rise and persistence of the high blood sugar curve, together with the well marked glycosuria, is due to the same cause. The blood urea in this case was slightly above normal, ranging from 40 to 46 mg. per 100 c.c. blood, and a two-hour renal study after the method of Mosenthal⁷ showed little evidence of renal involvement. This graph was puzzling to the writers. The test was therefore repeated after an interval of two weeks, with practically the same result. On each occasion the blood sugar on the day following the test returned to a level of approximately 0.11 per cent. It is probable that this case represents a very mild diabetes associated with arterial hypertension of endocrinal origin.

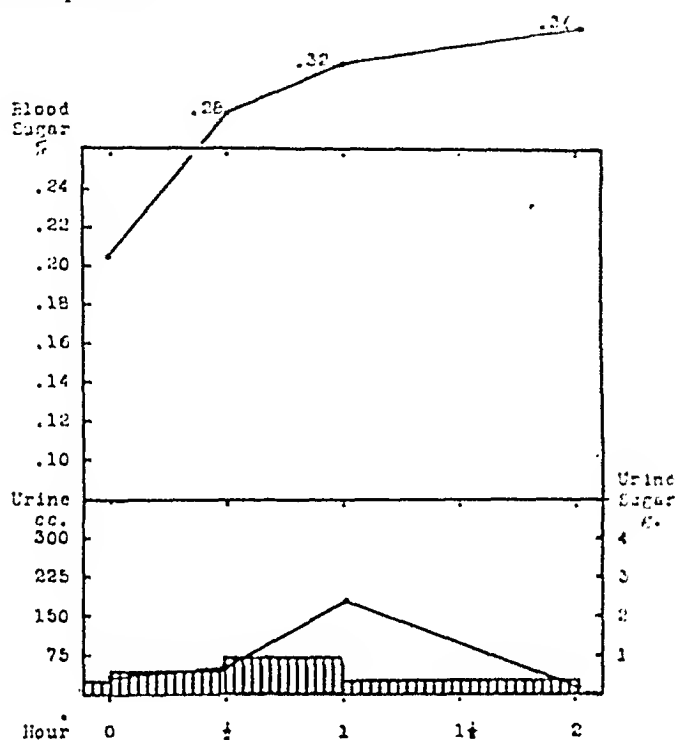
7. Mosenthal, H. O.: Arch. Int. Med. 16:733, 1915.

Chart 28.—Case 2440. Glucose utilization test in a woman aged 54. Mild diabetes; cardiac hypertension associated with endocrinal disturbance. Body weight, 165 pounds.



COMMENT.—This patient had a high blood sugar renal threshold—about 0.22 per cent. Her blood sugar level was affected appreciably by emotional influences as is shown elsewhere. This graph, together with the data afforded by other blood sugar estimations, leads to the conclusion that she has a mild diabetes.

Chart 29.—Case 2442. Glucose utilization test in a woman aged 65. Mild diabetes of recent origin in association with severe arterial hypertension. Body weight, 114 pounds.

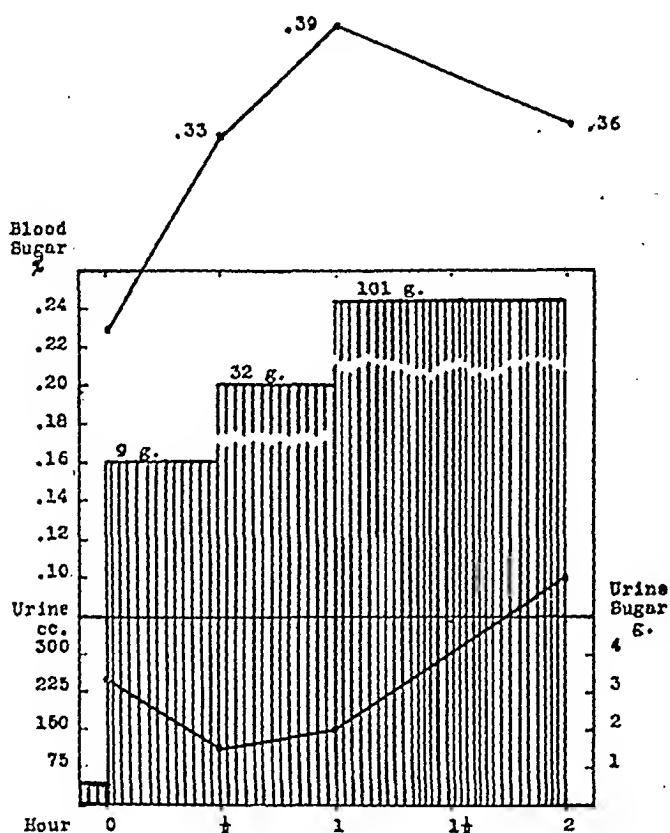


COMMENT.—Before the test represented in chart 29 was made, for seven days the patient had been on a diet containing approximately 180 gm. of carbohydrate and totaling about 2,000 calories. On this diet the blood sugar level ranged from 0.10 to 0.12 per cent. and she passed daily from 4 to 11 gm. of sugar in the urine. This would suggest an unusually low threshold. Five days after the test on the same diet, the patient was urine-sugar-free and her blood sugar level was 0.19 per cent., a rather high threshold. Urea studies and a Mosenthal² two-hour renal investigation indicate normally functioning kidneys. It seems quite probable, therefore, that there is some extrarenal factor influencing the blood sugar level in this case.

GLUCOSE UTILIZATION TESTS IN A SERIES OF CASES OF MODERATELY SEVERE DIABETES

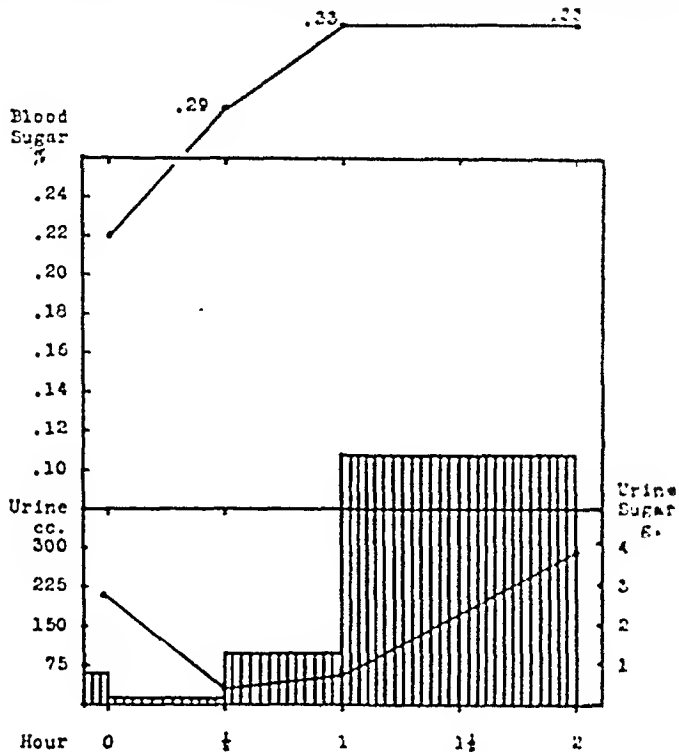
The following group of cases show more pronounced clinical evidence of diabetes, yet with the single exception of Case 2329, which has since terminated fatally, none of the patients can be classed as being more than moderately ill.

Chart 30.—Case 2279. Glucose utilization test in a woman aged 43. Moderately severe diabetes of one month's standing. Body weight, 128 pounds.



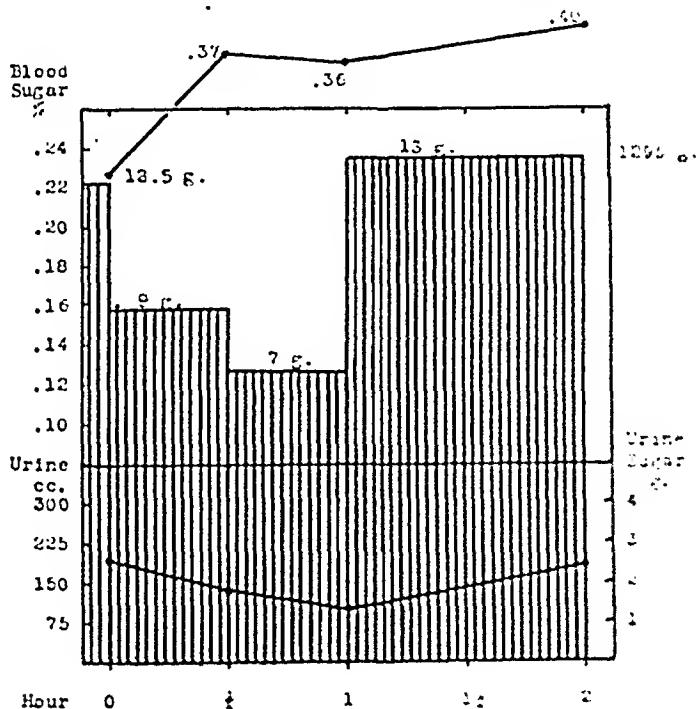
COMMENT.—The interesting feature of this case is the high renal threshold exhibited. On three occasions preceding the foregoing test, and at intervals of five days, blood sugar determinations were made and were, respectively, 0.20, 0.13, and 0.22 per cent. On each occasion the patient was urine-sugar-free so that the threshold must lie above 0.22 per cent., or, as shown in this graph, at 0.23 per cent.

Chart 31.—Case 1001. Glucose utilization test in a woman aged 56. Moderately severe diabetes of four months' standing. Body weight, 180 pounds.



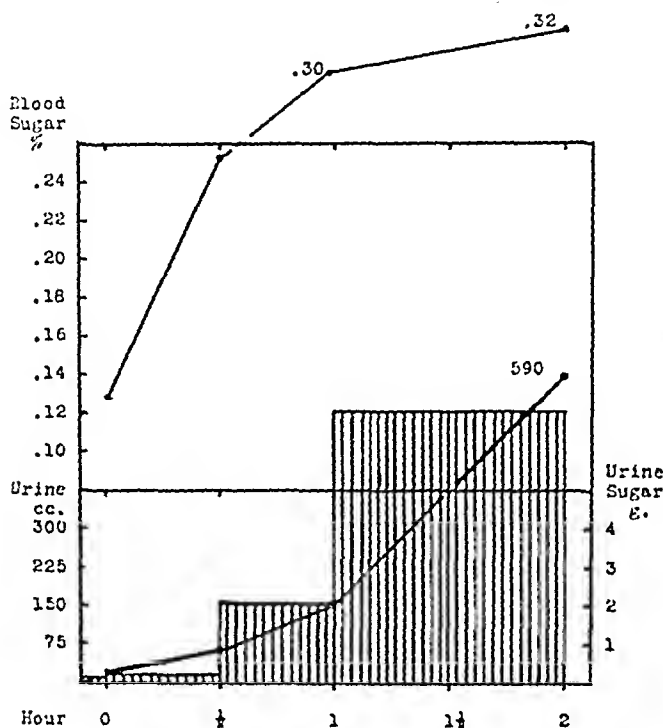
COMMENT.—This patient, like the preceding one, had a high renal blood sugar threshold and a high blood sugar level. The noteworthy failure of sugar utilization is evident in these cases.

Chart 32.—Case 2399. Glucose utilization test in a man aged 54. Moderately severe diabetes of one month's standing. Body weight, 134 pounds.



COMMENT.—This case represents the early stage of an acute moderately severe diabetes which yielded promptly to treatment. The graph shows strikingly the comparative degree of metabolic failure.

Chart 33.—Case 2329. Glucose utilization test in a woman aged 32. Severe diabetes of less than one month's standing. Body weight, 103 pounds.



COMMENT.—This patient had all of the clinical symptoms of rather severe diabetes, including thirst, polyuria, and loss of weight. In many respects she was quite a remarkable case. Throughout the period of observation of forty days she showed a rather low blood sugar and a severe acidosis, even when on a practically fat-free diet. The data of this interesting case are plotted elsewhere. It terminated fatally one month after the last observation.

CONCLUSIONS

1. The glucose tolerance and utilization test proposed by Hamman and Hirschman⁶ and as later modified by Janney⁵ is an extremely useful procedure in differentiating those but little understood metabolic disorders in which traces of reducing substance are excreted in the urine from renal diabetes and mild diabetes mellitus.

2. As a means of measuring the degree of disturbance in carbohydrate metabolism in hyperthyroidism and other endocrinal disorders, it is much superior to tests depending solely on the determination of urine sugar.

3. Many persons are rejected for life insurance and are treated as diabetics because of the occasional or even frequent finding in the urine of copper reducing substance. Tests on a series of these cases indicating a normal power to utilize glucose are here shown.

4. Renal diabetes is a definite physiologic disturbance, easily distinguishable by this procedure from true diabetes.

5. The sugar tolerance and utilization test is particularly useful in differentiating those cases of very mild diabetes in which there are exhibited no clinical symptoms of the disorder. The various degrees of failure of carbohydrate metabolism in the more evident cases of diabetes are most strikingly shown by this method.

THE EPIDEMIC OF INFLUENZA AT CAMP MERRITT, N. J.

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During the recent pandemic of influenza, September to November, 1918, several observations as to the nature and general character of the disease and of the epidemic have been made at U. S. A. Base Hospital, Camp Merritt, N. J. It is the purpose of the present work to present some of these observations with respect to: (a) the clinical and pathologic picture of influenza and bronchopneumonia; (b) the importance of secondary invaders in the latter part of the epidemic, and (c) the change in character of the latter part of the epidemic consequent on the activity of these secondary invaders.

In all the literature on this epidemic, both lay and scientific, certain distinctions have been made between influenza as such, and a concomitant or complicating bronchopneumonia. It has seemed to us more rational to regard this so-called "bronchopneumonia" not so much a complication as a severe manifestation of the disease itself. Christian¹ has recently discussed this same point. It is, however, convenient to employ the word "influenza" for the early stage and the word "bronchopneumonia" for the later stage of the disease.

From Sept. 19 to Nov. 6, 1918, 4,979 cases of influenza were treated at this hospital. Of these 4,979 cases, 1,015, or 20.4 per cent., developed bronchopneumonia, and of these latter, 31 per cent. died — a mortality for all the admissions of 6.3 per cent. It is unnecessary to say that all deaths were in this late or serious group and that the development of chest signs and symptoms enabled the diagnosis of bronchopneumonia to be made in each and every fatal case. Chart 1 shows the progress of the epidemic from day to day.

It is seen from Chart 1 that the incidence of new cases of influenza reached its height in about ten days after the start of the epidemic; that new cases of bronchopneumonia reached their maximum three days later; and that the summit of the death curve came nine days after

1. Christian, H. A.: Incorrectness of the Diagnosis of Death from Influenza, J. A. M. A. 71:1565, 1918.

A few of the early typical cases (perhaps 10 or 15 per cent.) presented a very faint pinkish macular eruption on the face, neck and anterior chest which often simulated the early eruption of measles, but which usually cleared up in about eighteen hours. The pharynx was usually red, at times showing small punctate hemorrhagic spots, but no enanthem or true Koplik spots were ever seen. Epistaxis was frequent, often severe. The lungs showed in a small proportion of cases a few râles at the bases, but this was by no means a characteristic finding.

The clinical course was rapid. In the majority of these cases, the temperature fell to normal, usually subnormal, within four days, leaving the patient still prostrated and weak. The pulse was not rapid; at the height of the disease it was full and showed a tendency to dirotism. Immediately after the fall in temperature the bradycardia was striking; observations of as low as fifty beats per minute being not infrequent.

Laboratory Findings.—In these early influenza cases, laboratory findings were disappointing.

Blood cultures on hormone gelatin broth³ (10 c.c. of blood in 100 c.c. of medium) were sterile in each of the nine cases studied.

Throat cultures planted on Loeffler's blood serum gave a mixture of organisms in each of thirty cases. Similar throat cultures from the same patients streaked on defibrinated blood infusion agar plates showed nonhemolytic streptococci in seventeen cases, in two of which they were associated with pneumococci, and in three others with gram-negative influenza-like bacilli. In four cases gram-positive diplococci predominated, and two showed only staphylococci.

Postnasal cultures were streaked on laked blood hormone agar³ plates and showed a mixture of organisms in seventeen; a predominance of gram-negative influenza-like bacilli in five; while in two there was no growth.

Total leukocytes were counted on the first day of admission in ten cases, and averaged 9,200 cells per cubic millimeter. On the fourth day, in the same patients, they averaged 8,500, at which time none of these patients had developed pneumonia. A study of the *sputum* was anticipated, but these patients in the early stage of the disease did not raise suitable sputum, in spite of the fact that coughing was often a definite symptom.

Treatment of these early "influenza" cases resolved itself into three objects: First, a vigorous attempt to dilute toxins, and promote elimination by forcing fluids and by providing free catharsis with

3. Huntoon, F. M.: Hormone Medium, J. Infect. Dis. 23:169, 1918.

castor oil or magnesium sulphate; second, a symptomatic relief of the headache and muscle pain with acetyl salicylic acid combined with alkali or with Dover's powder, and of the cough with expectorants or sedatives (codein) as indicated; and third, the very important and close study of the chest to determine at the earliest moment the development of pathologic physical signs in the lungs, with the view not only of changing the treatment, but, more important, of isolating the patient in a pneumonia ward as soon as possible.

BRONCHOPNEUMONIA

Clinical Picture.—Quite as typical in its clinical unity as influenza proper was the serious manifestation of this infection spoken of as "bronchopneumonia." We wish to describe a set of symptoms and signs with the attending pathologic changes which mark the severe stages of influenza. After the first symptom of influenza, the average time of onset of this manifestation was 4.03 days in a series of 726 recovered cases, and 5.7 days in a series of forty-seven fatal cases.

The diagnosis of bronchopneumonia was made as follows: As was said in the foregoing, the uncomplicated upper respiratory tract influenza was associated with a fall in temperature, pulse and respiration to normal on the second, third, or, more usually, on the fourth day of the disease. In the bronchopneumonia cases, however, the temperature maintained itself or even rose higher at this time, the pulse became rapid, and of still greater significance, the respiratory rate, which had been between 20 and 24, now ascended, reaching anywhere from 28 to 50 per minute; cyanosis became quite noticeable, cough more severe, and physical examination of the lungs revealed a most constant finding, namely, one or more collections of small moist râles, patchy in distribution, usually located at the bases posteriorly. At this stage, dulness to percussion and the characteristic high-pitched bronchial expiration were usually lacking. On the contrary, there was frequently a diminution or even a suppression of breath sounds in the area affected. Experience soon taught us that in the following twenty-four or forty-eight hours signs of consolidation would appear in an area so affected. The heart, pericardium and abdomen proved uniformly negative.

The clinical picture now became characteristic. The patient was severely prostrated and apathetic: cyanosis of lips, cheeks and finger tips, with dyspnea, was impressive, the severe cough produced a glairy mucous sputum containing a small amount of purulent material; it had not the viscid tenacity of the sputum seen in lobar pneumococcus pneumonia. Blood in the sputum was a frequent finding; it ranged from a mere streaking to a considerable amount, and was reddish or

dark reddish in color, and had not the orange rusty tint seen in lobar pneumonia. Occasionally considerable amounts were expectorated, giving evidence of the hemorrhagic extravasation going on in the pulmonary tissues. Epistaxis, often seen in the earlier stages of the disease, now became quite marked, occasionally even alarming. Headache and chest pain require mention: the latter a more or less constant substernal pain apparently due to the intense acute tracheobronchitis, the former a continuation of the pain of the milder stage, and probably due to cerebral congestion.

In from twelve to seventy-two hours as the patient became more acutely ill, the cyanosis deepened and dyspnea became more marked. Symptoms of the profound intoxication now dominated the picture: abdominal distention; urinary retention; sordes on lips and teeth, and dry, parched, heavily coated tongue with foul breath appeared. Symptoms referable to the central nervous system were at times seen, as twitching of the muscles of the fingers, forearms and face. In this connection the delirium which appeared in all of the fatal, and in a good many of the recovery cases deserves mention. It took on the form either of an active, even maniacal occupational delirium, or more usually the low mumbling type described by the old writers as being associated with the asthenic fevers. Nausea and vomiting were occasionally seen. Jaundice was a rare symptom, probably depending on an increase in the viscosity of the bile and therefore obstructive in origin.

The temperature, pulse and respiration curves differed in the fatal and recovery patients. The fatal cases had a short course (Chart 2); in a series of thirty-nine such cases the duration of the pulmonary involvement averaged only 4.7 days. The temperature curve seldom assumed the sustained plateau so common in lobar pneumococcus pneumonia, but was rather of an irregular, remittent type, ranging from 99 to 105 or even to 107 F.

The pulse rate was usually considerably slower in these primary cases than would ordinarily be expected in a lobar pneumonia of similar severity. However, a stepladder rise in the pulse rate was of serious prognostic import, the continuance of this rise for over three days almost invariably indicating a fatal outcome. Irregularity of the pulse was seldom seen.

Of greater value than either the temperature or the pulse was the respiratory rate, which was always raised. Here again a climb in the rate, sometimes precipitous, usually more gradual, presaged death.

The systolic blood pressure was normal in the acute stage of the disease, the diastolic was at times often as low as 55. With the drop in temperature the systolic pressure also declined, the diastolic pres-

sure remaining low. These relatively low pressures were then maintained for several days, during the period of subnormal temperature and slow pulse, when they slowly recovered. No other marked or consistent observations were made on blood pressure, nor were essentially different observations made in the fatal and recovered cases. Readings within twenty-four hours of death were made in several instances at a time when the pulse was very rapid, but no additional

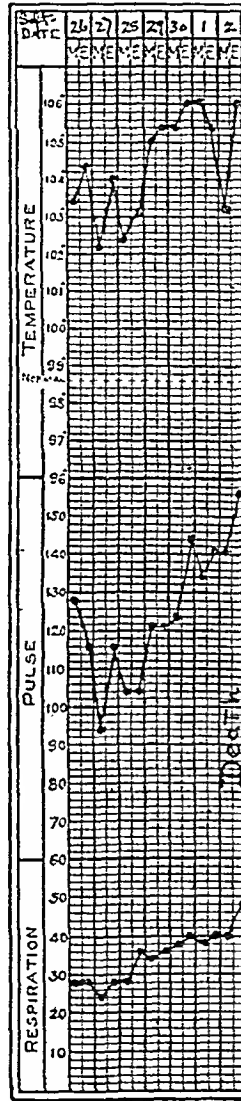


Chart 2.—Temperature, etc., early fatal case.

fall was seen. From these observations we may deduce that in this disease vasomotor tone is depressed, but that the heart's strength remains good to the end.

Total leukocyte counts were made in many cases, but no consistent findings were observed except that in the cases of primary influenzal bronchopneumonia the average count was low (5,000 to 15,000 cells per cubic millimeter). The presence of the hemolytic

streptococcus tended to increase this average count but slightly, although the individual counts varied from 5,000 to 30,000 or even higher. Several cases were observed with counts below 2,000 cells, all of which were fatal.

In a small series of these bronchopneumonia cases the coagulation time of the blood was determined and found normal. The urine showed, as a rule, a trace of albumin with granular and hyaline casts.

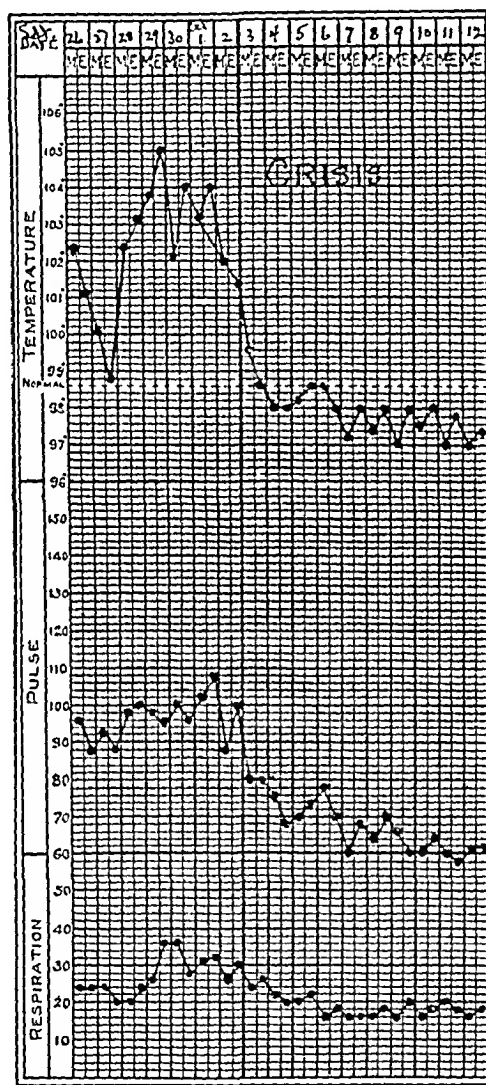


Chart 3.—Temperature, etc., crisis.

Red blood cells were found frequently. No other evidences of renal insufficiency were noted.

In the patients who recovered, the following interesting facts stood forth. In a series of twenty-five such patients, sixteen, or 64 per cent., had a temperature fall by "crisis" (Chart 3); that is, a drop from 102 or 105 to normal in forty-eight hours or less, whereas nine, or 36 per cent., had a defervescence by lysis. In these crisis cases a

decline occurred usually on the third day of the pulmonary involvement; in the lysis cases, usually on the fourth day, in which group an overage of 5.5 days then elapsed before the normal base line was reached.

The pulse and respiratory rate usually dropped in accordance with the temperature, although not infrequently the pulse rate fell to below the normal, reaching 40 or 50 beats per minute for a few days. The respiratory rate occasionally remained considerably elevated for days before it fell to normal. A very interesting corollary to these findings was that, considering the entire disease, by the time the temperature chart had completed its first week's cycle, the patient had either started on his defervescence or else the pulse and respiration had begun their ominous, fatal rise. As a consequence, the black line at the end of the first week on the temperature chart came to be called the "Dead Line."

We have already referred to the physical examination of the lungs at the beginning of bronchopneumonia and emphasized the consonanting râles most marked at the lung bases behind. In the more severe cases, moist and dry râles were generalized, being especially marked at the bases and over the interscapular regions. Frequently patients died, some within two days, with no further evidence of pulmonary invasion than these râles. With Christian¹ we have never seen moribund cases without definite chest signs or symptoms. With the advance of the disease, dulness increased, fremitus, bronchovesicular, and finally bronchial breathing were heard most commonly at the bases, especially at the right. A pleuritic friction rub occurred infrequently; signs of pleural effusion were never found. As death approached, the larger moist râles of pulmonary edema dominated the picture.

Bacteriologic findings in these influenzal-bronchopneumonia cases will be discussed later.

Complications and sequelae of this severe infection in a series of 705 cases include:

	No. Cases		No. Cases
1. Otitis media, acute.....	28	6. Parotitis	7
2. Tonsillitis, acute follicular....	15	7. Phlebitis, acute.....	5
3. Relapse	12	8. Sinusitis, frontal, acute.....	3
4. Laryngitis, acute.....	8	9. Emphysema, subcutaneous.....	3
5. Abscess, subcutaneous.....	5	10. Epistaxis, very severe.....	2

Of the seven cases of parotitis, four were clinically simple mumps, while three patients developed such extreme signs of inflammation (heat, redness and swelling) that their parotids were incised. A small amount of pus was evacuated in two cases, one being bilateral. All three patients recovered promptly.

The cases of relapse have been interesting. The diagnosis has been made only in those cases in which the temperature, pulse and respiration not only fell to normal or below 98.6, 70 and 20, respectively, but remained so for at least forty-eight hours. The second attack usually began suddenly in from two to eight days after the normal temperature had been reached. Following a shorter intermission, it

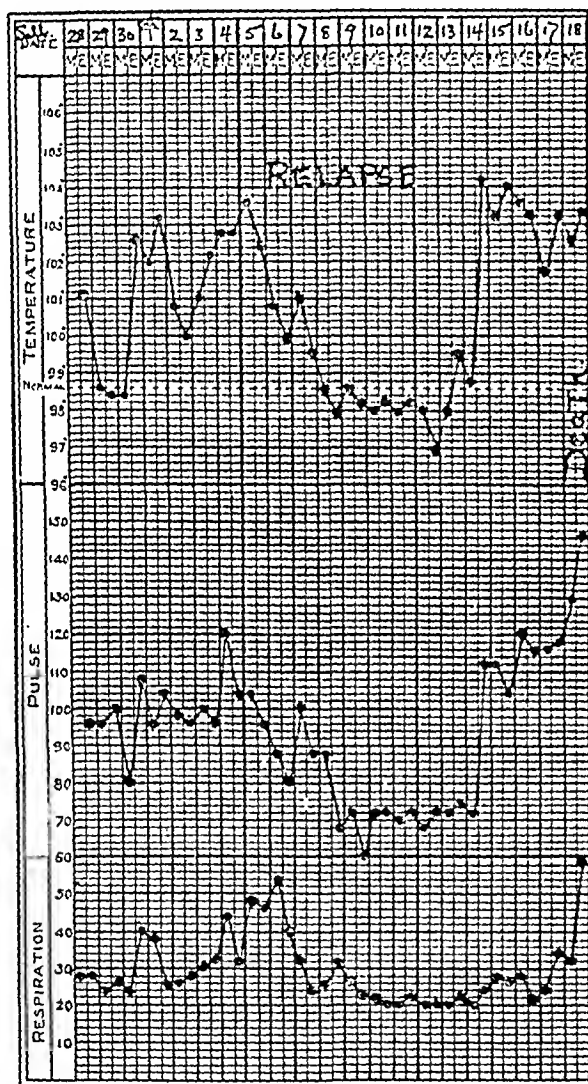


Chart 4.—Temperature, etc., relapse.

was more apt to be severe than after a longer one. On the whole, relapses have been very serious, the patient often dying within four days after the new rise of temperature, with a renewal in aggravated form of all the described symptoms, and usually on physical examination showing new areas of lung involvement. Chart 4 is typical. When the onset of the relapse is delayed, we have noted that in the interval the patient did not exhibit the sense of well-being with

increased appetite, so common in the recovered cases immediately after the fall in temperature.

It is unfortunate that insufficient data are available on the sputum bacteriology of the primary bronchopneumonia and of the relapse to compare them, and thus to decide whether these relapses are true reinfections or are instances of the secondary invasion of lung tissue already weakened. A few cases have shown different organisms in the two attacks.

"Unresolved pneumonias" have been somewhat frequent. Of 635 convalescent patients, 121, or 19 per cent., have shown râles with occasionally slight dulness and harsh breathing over the site of the original lung involvement, persisting for two weeks after the fall in temperature. While no figures are available we believe that practically all of these patients clear up entirely within from four to six weeks after defervescence.

Toward the end of the third week of the epidemic, as seen at this hospital, surprising changes took place. Reports from the laboratory showed an ever-increasing proportion of the hemolytic streptococcus in the sputum. In the early days of the epidemic it was difficult to obtain satisfactory specimens of sputum for study; the cough in the pure "influenza-bronchopneumonia" is usually unproductive of any definite purulent or mucopurulent plugs of sputum, so that washing the sputum was practically impossible, and results could be obtained only by streaking the crude material on blood agar plates.

Chart 5 shows the curves of the daily number of total sputum examinations, as well as the number of each type of organism found. These facts stand forth: the hemolytic streptococcus was at first present in inconsiderable numbers, but in the third and fourth weeks its curve closely approximated the curve of the total examinations. The influenza bacillus at first outnumbered the hemolytic streptococcus, but in the third week, its curve fell below the curve of the latter organism and remained below throughout the epidemic. The pneumococcus curve, in a general way, resembles the influenza curve, not only in their common relationship to the hemolytic streptococcus, but also in that their curves run an essentially parallel course.

Curiously enough, it was recognized that the streptococcus patients seemed to "do better" or at least as well as did the other patients, and further, that the death rate in proportion to the daily admissions seemed to fall markedly. Chart 6 illustrates these facts and demonstrates that, of the patients who entered the ward in the first five-day period, 65 per cent. died, while at the end of the epidemic, none of the patients admitted in the last three five-day periods died. Further-

more, the individual ward was losing its homogeneous appearance. The clinical course of the individual patient was no longer true to the type described.

This sudden and remarkable change in the clinical picture, in laboratory findings, and in necropsies is to be explained by the invasion of secondary organisms and the construction of a new pathology.

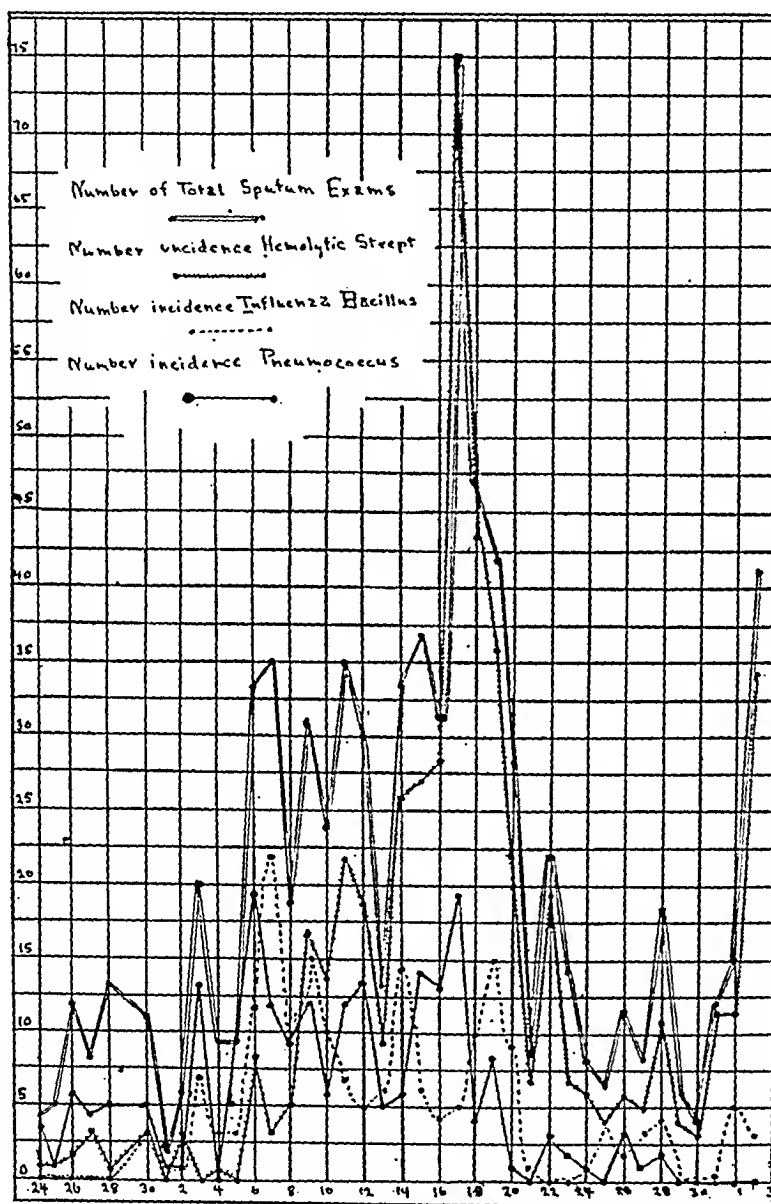


Chart 5.—Daily incidence of sputum organisms.

Treatment.—Treatment of the influenzal bronchopneumonias was purely symptomatic, although stress was laid on keeping the intake of total fluids as great as possible. Digitalis, camphor and occasionally strychnin were used in an attempt to control the rising pulse rate; they seemed at times to be effective. When the patient was unable

for any reason to take fluids well and became "dried up," with dry tongue and skin, tap water was given by rectum, and in a few cases salt solution (always made up with freshly distilled water) was injected intravenously in daily doses of 500 c.c. each. On advice that a vaccine containing in 1 c.c., 100 million mixed pneumococci together with 100 million streptococci, 100 million staphylococci, and 100 million influenza bacilli gave good results in these acute cases at U. S. A. General Hospital 1 in New York City, it was tried here on seventeen patients in doses injected intravenously as follows: First day 1 c.c., second day 2 c.c., and third day 3 c.c. The results were very

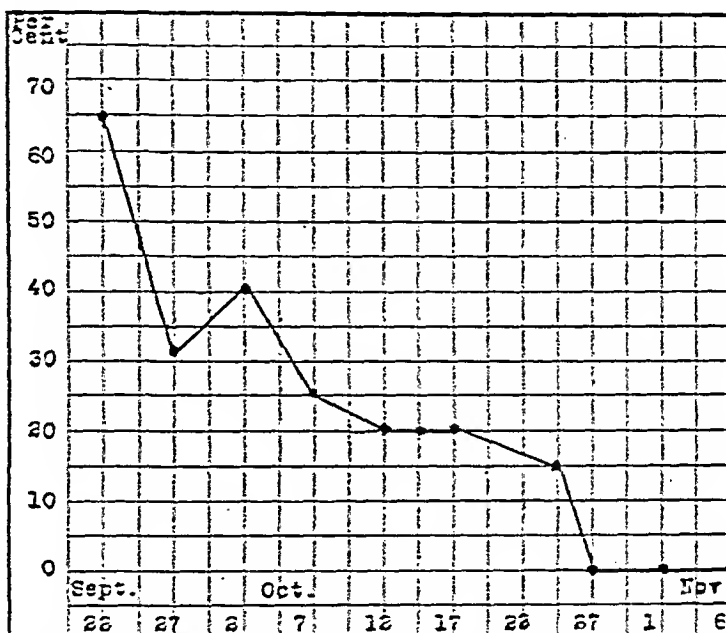


Chart 6.—The variation according to the stage of the epidemic in the average percentage death rate of patients admitted to three typical pneumonia wards during consecutive five-day intervals.

disappointing. Of 17 treated patients, 5 died (29.4 per cent.). Of 26 other patients who entered the ward on the same day as the treated, and therefore served as controls, only 5 died (19.2 per cent.). Furthermore, the total days of fever averaged 11.5 in the treated patients, but only 9.8 in the control series, so that in the vaccinated group the mortality was higher and the duration of illness was longer.

Many of the cases at this time were similar to the now familiar post-measles streptococcus bronchopneumonia described by Cole and MacCallum.⁴ The course of the disease became considerably lengthened (Chart 7 is typical); the patients no longer appeared overwhelmed by a virulent toxemia. Beside showing the hemolytic strep-

4. Cole and MacCallum: Pneumonia at a Base Hospital. J. A. M. A. 70:1146, 1918.

tococcus in such numbers, the sputum became more profuse and purulent.

The most striking change, however, was that whereas in the influenzal type of bronchopneumonia already described, pleural effusions were never encountered, they now became comparatively common complications. Pericarditis was also noted. It is beside our

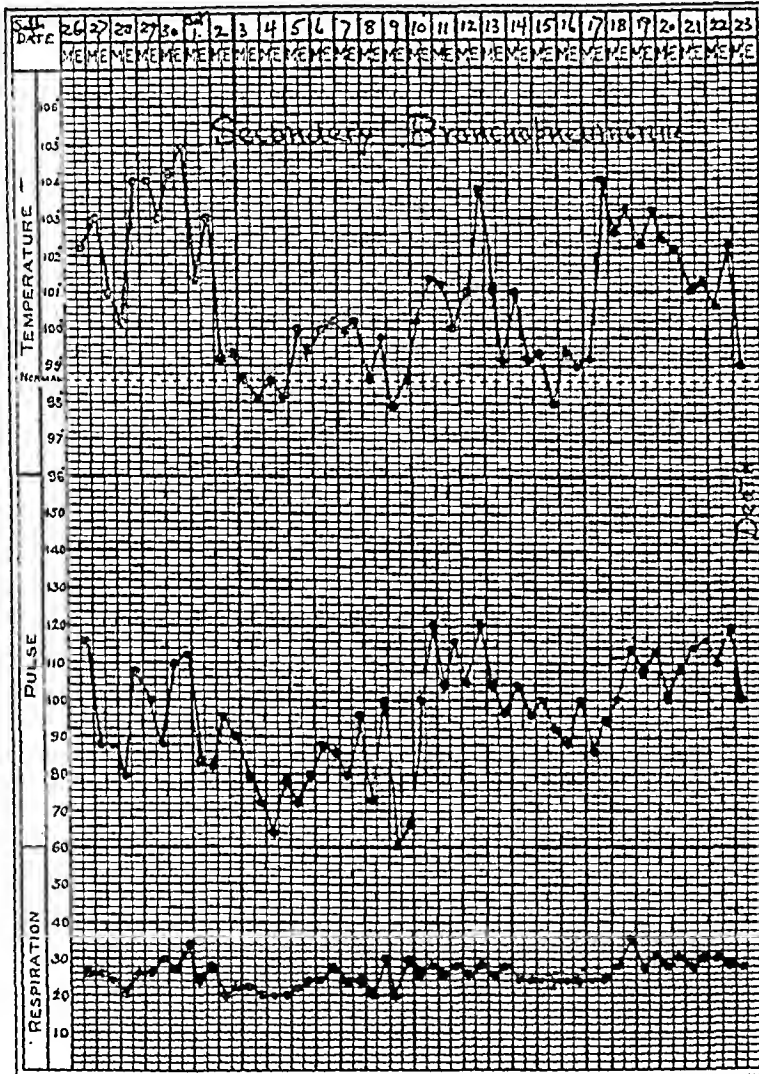


Chart 7.—Temperature, etc. Later case with prolonged course.

purpose to describe this syndrome in further detail, except to speak of our experiences with empyema.

EMPHYEMA

By empyema we have reference to the pleuritic effusion complicating bronchopneumonia, regardless of gross appearance or of bacterial flora. The bacteriology of fifty such fluids coming to the laboratory of the hospital from October 1 to November 9 was studied

(Table 1). Brooks and Cecil⁵ have studied eighty cases of empyema at Camp Upton, occurring during the months from October, 1917, to and including April, 1918. A considerable number of their empyemas developed in pneumonia following influenza, tonsillitis and other mild infections. The comparison of their results with ours is interesting.

It will be seen in both series, that a little over half the cases were due to the hemolytic streptococcus. On the other hand, Cole and MacCallum found the hemolytic streptococcus in all the twenty-six cases of empyema complicating their series of post-measles bronchopneumonia at Fort Sam Houston.

TABLE 1.—THE RESULTS OF BACTERIOLOGICAL EXAMINATION OF FIFTY PLEURAL FLUIDS COMPARED WITH RESULTS FOR EIGHTY FLUIDS AS REPORTED BY BROOKS AND CECIL⁵

	Per Cent. of Our 50 Cases Showing the Organism	Per Cent. of Brook's and Cecil's 80 Cases
Hemolytic streptococcus.....	52	53.7
Sterile.....	22	18.7
Pneumococcus Type I.....	6	3.7
Pneumococcus Type II.....	22	5.0
Pneumococcus Type IV.....		10.0
Nonhemolytic streptococcus.....	4	7.5
Staphylococcus aureus.....	..	1.2

In the study of etiology, a comparison of the bacteriology of chest fluid with the sputum in the same patient is important. Of twenty-seven instances in our series, in which organisms were determined in both fluid and sputum, seventeen, or 63 per cent., showed the same organisms, while ten, or 37 per cent., showed different organisms. Table 2 gives our findings in detail.

In the series of Brooks and Cecil 70.7 per cent. showed the same organism in fluid and sputum.

This brings up the question as to the value of the determination of sputum organisms in reflecting pulmonic or pleural infection. While the series of cases studied here is small, none the less, an inconsistency of about 35 per cent. in findings might be interpreted as a considerable factor of error. However, the manifold sources of origin of sputum and the mixture of infections so apt to occur in the respiratory tract should be considered.

From a study of our necropsy findings we hope to be able to show that mixed infections in the lungs account for the finding of one organism in the sputum and another in the pleural fluid. In our series, all empyemas developed during the acute stage of the bronchopneumonia.

5. Brooks and Cecil: A Study of Eighty Cases of Empyema at Camp Upton, Arch. Int. Med. 22:269, 1918.

Physical Signs of Pleural Exudate.—The study of the physical signs has been, as in Brooks and Cecil's series, very disappointing, and we also "have unlearned far more physical signs of pleural fluid than we have perfected." The diminished expansion of the base, the diminution, or loss of tactile fremitus, and most important, the flat percussion note still constitute the more reliable signs. Diminution of the breath and voice sounds and the ready audibility of râles are so misleading that we have learned to almost disregard them. Displacement of the heart has been inconstant. While the roentgen ray has been of immense aid in localizing the smaller pockets of fluid, there is no doubt that the presence or absence of fluid is best established by tapping, and numerous taps may be necessary.

TABLE 2.—COMPARISON OF BACTERIOLOGY OF CHEST FLUID AND SPUTUM IN THE SAME PATIENT

Same Organism in Fluid and Sputum	Different Organisms in 10 Combined Examinations of Fluid and Sputum						
	Fluid			Sputum			
	Hemo- lytic Strepto- coccus	Non- hemo- lytic Strepto- coccus	Pneu- mo- coccus IV	Hemo- lytic Strepto- coccus	Non- hemo- lytic Strepto- coccus	Pneu- mo- coccus IV	Pneu- mo- coccus Undeter- mined
Hemolytic strepto- coccus.....	2		1*		1*		3
Pneumococcus I....	3				2		
Pneumococcus IV....	4†				4†		
Pneumococcus IV....	5		7	7	5†		
Pneumococcus IV....	6			8	6		
Total.....	17	8	10†		10	9	

* Numbers refer to the ten patients in this section.

† Indicates that the influenza bacillus was also found.

At the necropsy table an explanation was sought as to why the classical auscultatory signs of fluid were so often lacking. The answer to the question we believe is that whereas in the typical pleural effusions of tuberculosis or lobar pneumonia the lung is pushed up toward the hilus by the fluid, here the tendency toward sacculation is so strong that the lung very frequently is adherent over larger or smaller areas of the parietal chest wall, and we believe that lung tissue, so adherent and compressed by the surrounding fluid, makes an admirable conducting medium for the passage of breath and voice sounds.

The various and peculiar sacculations of the fluid at the base, between the lobes, between the pleura and pericardium, in the anterior mediastinum, etc., represent a later stage of this process of sacculation and render the localization of such fluid extremely difficult. The

encapsulation of these fluids was often beautifully shown by the roentgen ray, and was found by it to be more frequent than free fluid in large amounts.

Vaughan and Schnabel⁶ have recently discussed the pathology and diagnosis of empyema in cases with and without an antecedent measles and have noted the tendency to the formation of pus pockets.

The treatment of these secondary infections largely concerns itself with the determination of the presence or absence of empyema. When pus is found we believe, with most of the recent writers, that operation should be delayed, not only in order that the pus may be well walled off, but that consolidated areas in the lung itself may be resolved as much as possible, so that the patient's general condition will be as favorable for operation as may be. With a continued typhoid-like temperature it is often very difficult to estimate whether its continuance is due to a persistent involvement of the lung or to pus. Afebrile empyemas are not uncommon. In such cases the pulse and respiration remain more rapid than in truly convalescent patients.

NECROPSY FINDINGS

Necropsy findings in the different periods of this epidemic varied considerably.

Douglass Symmers⁷ has described the pathology of acute influenzal bronchopneumonia. We believe that capillary damage with resulting hemorrhages represents the keynote of the pathology and explains not only the wet, bloody, soggy lung seen at necropsy, but also the bleeding from nose, bowels or kidneys which occur clinically.

In this acute disease, the upper respiratory tract is acutely inflamed, the mucosa throughout being injected, swollen, succulent, with hemorrhages in places. The bronchial lymph glands are enlarged, and on cut section appear injected and hemorrhagic.

Pleural effusions, except for a small amount of sanguineous fluid in a few cases, were never found, and although the visceral pleura frequently lost its glossy sheen, fibrin in any considerable amounts was absent. The lungs were the site of the most important lesions: the involved lobes, especially the lower, presented a deep blue-red appearance and seemed bulky; while on palpation they were heavy and soggy, without, however, the solidity of pneumococcus hepatization. On section, the involved area was almost blue black and literally dripped a frothy, bloody fluid in large amounts, in marked contrast

6. Vaughan and Schnabel: Pneumonia and Empyema at Camp Sevier, Arch. Int. Med. 22:440, 1918.

7. Symmers, D.: Note on the Pathology of Influenza, New York M. J. 108:621, 1918.

to the "dryness" of lobar consolidation. No fibrin plugs came away with the knife. Areas of hemorrhagic infarction were fairly frequent. The anterior borders of the lungs were almost invariably emphysematous and uninvolved. A few cases showed some interstitial emphysema in the lung tissue, which led to a generalized subcutaneous emphysema in the three cases already mentioned under complications. Pneumothorax was found once.

In the less severe cases, only parts of lobes were involved and they appeared like the areas of marked congestion seen in hypostatic pneumonia. In the slighter involvements, patches of engorged or congested lung tissue were noted.

In these early acute cases the absence of pus deserves repeated emphasis. The pericardium was normal, the heart occasionally revealed a right-sided dilatation, which was, however, rarely marked. The endocardium was normal as was also the aorta.

The stomach and intestines occasionally revealed small areas of capillary hemorrhage in the mucosa. While the gallbladder was normal, the viscosity of the bile therein was markedly increased in a few cases to the consistency of thin paste. We believe that the flow of such bile can be retarded to the extent of producing an obstructive jaundice. Mere mention may be made of toxic degeneration in the liver, and the congestion of kidneys, spleen and brain.

Microscopic Study.—The alveoli and bronchioles contained an exudate composed mainly of red blood cells and serum; polymorphonuclear leukocytes with desquamated epithelial cells occurred to a lesser extent. Fibrin was not found.

In the areas of advanced disease, the structure of the alveolus was lost; large numbers of erythrocytes and a large amount of serum with a moderate number of leukocytes "packed" the alveoli and smaller bronchi. The capillaries were engorged and stood out. The bronchial walls were edematous.

In less advanced stages, the same cellular elements in the same proportion were found in lesser numbers and were at times grouped about the bronchi.

The heart muscle showed but slight granular degeneration. The kidneys showed considerable albuminous degeneration of the tubular epithelium, with granular debris in the lumina. The glomeruli were frequently congested.

The liver showed varying degrees of granular degeneration, the spleen, of congestion.

These findings indicate that the term "bronchopneumonia" is a misnomer, but in view of its general use, we hesitate to suggest a new term for this picture.

Secondary Bronchopneumonia.—With the advent of the secondary invaders, the pathology changed. Pus formation and the resemblance to post-measles bronchopneumonia were noted. The mucous membrane of the upper respiratory tract was bathed in a mucopurulent exudate, beneath which the mucous membrane was acutely inflamed. Edema of the glottis and ulceration of the vocal chords were seen.

The pleura in these cases showed the most important and most striking lesions. Larger or smaller areas of the visceral and parietal pleura were very often coated with a heavy, shaggy coat of fibrin, which by adhesions to the contiguous lung tended to form the pockets of pus which were so common. These encapsulated empyemas have not infrequently been multiple, in the positions already noted. It is of interest that often different pockets contained fluids of different color and consistency, ranging from a cloudy-amber to a greenish-yellow pus, and frequently showing shreds of fibrin.

The lungs revealed a condition of bronchopneumonia which can be divided into stages: first, beginning bronchopneumonia, where small reddened nodular areas stood forth on cut section, their center being a small bronchus which exuded pus, between which fairly normal crepitant lung was found; second, these same nodular areas became larger, grayish in color, and on pressure exuded considerable yellow pus from both bronchi and lung tissue; third, the spread and confluence of these areas produced a large area of consolidation—the pseudolobar bronchopneumonia of Osler,⁸ and fourth, larger or smaller areas underwent necrosis with abscess formation, the affected tissue becoming soft, mushy, and losing its distinctive markings. Atelectasis and septic infarction need only be mentioned: the former common, the latter occasional.

The pericardium revealed not infrequently an acute serofibrinous inflammation: an acute vegetative endocarditis was seen but once; otherwise the heart and aorta were consistently “negative.” The spleen in these cases was often enlarged, its pulp quite degenerated, mushy and necrotic.

The other viscera revealed no pathologic changes.

Microscopic Study.—In contrast to the hemorrhagic exudate of the former picture, the alveoli and bronchi in these cases contained an exudate of polymorphonuclear leukocytes and serum, whereas red blood cells were insignificant. The bronchial walls were edematous, infiltrated with polymorphonuclear leukocytes; their epithelium was frequently desquamated. While in less advanced areas polymorphonuclear cells were grouped about the bronchi, later this distinction was

8. Osler: Principles and Practice of Medicine, Ed. 8, Appleton Co., New York.

lost. In some of the specimens the number of large mononuclear (epithelioid) cells has been quite astonishing; these cells equalling, if not outnumbering, the polymorphonuclear leukocytes.

While actual giant cells were rarely seen in such specimens, a distinct tendency toward their formation was not infrequently noted.

Whether the presence of these large mononuclear cells is a part of cellular resolution indicative of a strong phagocytic process is problematical; however, the presence of a good many pigment-bearing cells in certain areas leads toward the belief that these mononuclear cells are capable of considerable phagocytic activity.

In certain cases edema was considerable.

TABLE 3.—A COMPARISON OF THE BACTERIOLOGY OF THE LUNGS BETWEEN THE FIRST FIFTEEN AND THE LAST THIRTY OF FORTY-FIVE CONSECUTIVE NECROPSIES

	First 15 Cases From Sept. 23 to Oct. 8	Last 30 Cases From Oct. 9 to Nov. 18
Hemolytic streptococcus alone.....	0	10
Hemolytic streptococcus and pneumococcus.....	1	0
Hemolytic streptococcus, pneumococcus and influenza B.	1	3
Hemolytic streptococcus and influenza bacillus.....	2	6
Total hemolytic streptococcus.....	4 (26.4%)	19 (63.7%)
Influenza alone.....	3	0
Influenza and pneumococcus.....	5	4
Influenza and hemolytic streptococcus.....	2	6
Influenza, hemolytic streptococcus and pneumococcus.....	1	3
Influenza and nonhemolytic streptococcus.....	0	1
Total influenza.....	11 (72.6%)	14 (57.2%)
Pneumococcus alone.....	2	4
Pneumococcus and hemolytic streptococcus.....	1	0
Pneumococcus and influenza bacillus.....	5	4
Pneumococcus, hemolytic streptococcus and influenza B.	1	3
Total pneumococcus.....	9 (59.5%)	11 (34.3%)
Nonhemolytic streptococcus alone.....	1	2
Nonhemolytic streptococcus and influenza bacillus.....	0	1
Total nonhemolytic streptococcus.....	1 (6.6%)	3 (9.9%)

In the more advanced areas cells in various stages of degeneration, indicating necrosis, were found.

Our studies of the lungs of post-measles bronchopneumonia have not been extensive enough to allow of any comparison to their pathology, as described by Cole and MacCallum.

The kidneys and liver have shown extensive acute granular degeneration: the spleen, cellular necrosis with dilatation of the lymph spaces (producing the large mushy spleen).

Between the acutely engorged hemorrhagic lung of the pure influenza-bronchopneumonia, on the one hand, and this more advanced, less acute process associated with pus formation on the other, were

all stages of transformation and all combinations. In fact, in many of our cases, a mixed type of lung infection was found. The invasion by the secondary organisms is in no sense invariably productive of a pure type. We believe that this accounts for the discrepancy found on bacteriologic examinations of sputum and chest fluids. In measles, on the other hand, the invaders are almost invariably the hemolytic streptococcus, and as a consequence, a purer pathologic type of interstitial or lobular pneumonia is produced and the complicating empyema is naturally almost invariably due to the hemolytic streptococcus.

Bacteriology.—The bacteriologic findings in these lungs are shown in Table 3. Emphasis is to be laid on the fact that while the hemolytic streptococcus was found in only 26.4 per cent. of the first fifteen necropsies, in the last thirty it was found in 63.7 per cent. In contrast to this, the influenza bacillus was found in 72.6 per cent. of the first fifteen necropsies, and in 57.2 per cent. of the last thirty.

CONCLUSIONS

1. From our own observations and those of others, we believe that we are dealing with a severe, highly contagious, acute, infectious disease. As to the cause of this disease, we have been able to add nothing to the findings of others. The frequent finding of Pfeiffer's bacillus in sputa and in lungs at necropsy is interesting, but not peculiar to this disease.

2. We believe that we are dealing with one essential disease which at first is a clinical entity, but that the primary symptomatology and pathology is complicated in certain cases by changes due to secondary invading organisms. Our reasons are: first, the disease occurs in epidemic form; second, typical cases are clinically alike, and third, the clinical picture is distinct and is so characteristic of this disease as to differentiate it from that of any other disease.

3. It is our experience that all fatal cases develop "bronchopneumonia" before death, and we believe that this "bronchopneumonia" is but a later manifestation of pure influenza, because: first, the lung signs develop in many cases during the primary influenza; second, the pathologic picture of the lungs in influenzal bronchopneumonia is distinctly characteristic, being quite unlike the picture seen in other forms of pneumonia. We have referred to the misuse of the term "bronchopneumonia."

4. The later weeks of this epidemic were characterized by the invasion of numerous secondary organisms, among which the hemolytic streptococcus occurred in largest numbers. No one of these organisms occurred consistently enough to justify the assumption of a pure pathology. Furthermore, these invading organisms produced

a change in the clinical and pathologic picture of the individual case resulting in a mixed type of pulmonary lesion. The development, nature, and diagnosis of empyema as a complication was here characterized, not by free pus in the chest, but more often by the formation of pockets of pus.

5. The similarity between influenza, as observed here, and measles is striking. Both diseases occur in epidemic form and are very highly contagious. The clinical course is similar. Both diseases have a sudden onset, with fever high in degree and short in duration. In the acute stages, the upper respiratory symptoms, with coryza, lachrimation and an aggravating, unproductive cough are much alike. The occasional faint, evanescent rash in influenza is often suggestive of measles. Both diseases have a low total leukocyte count. The greatest similarity, however, lies in the predisposition of patients with, or convalescent from influenza, to develop secondary infections of the lung and pleura. Attention is called to this similarity in order to stimulate further study on the etiology of both diseases.

Our thanks are due to Major Edward S. Rimer for his interest, and to Capt. Raymond Sanderson and his laboratory staff for placing at our disposal laboratory data without which the writing of this paper would have been impossible.

LEUKOCYTIC STUDIES ON SOLDIERS WITH IRRITABLE HEARTS *

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INTRODUCTION

This study of the morphology of the blood with reference to the leukocyte in cases of "irritable heart of soldiers" was suggested by the report of the Medical Research Committee, under the direction of Dr. Thomas Lewis.¹ In comparing this work to that which has been published in England, it must be borne in mind that the cases studied in the Hampstead Military Hospital may have differed from the type observed in U. S. Army General Hospital 9, at Lakewood, N. J. However, the basis of this work was a large series of selected cases in which no organic lesion of the heart and no foci of active infection were found by careful and repeated examination. The following are the more common symptoms given by these patients:

1. Breathlessness, produced by slight exertion.
2. Precordial pain, coming on suddenly after exertion, spreading over the left chest.
3. Fatigue, with or without exertion.
4. Vertigo, and occasionally fainting spells.

The studies here reported were undertaken in the following order:

1. A series of cases with "irritable hearts" was studied with no attempt at subdivision into special groups. The leukocytes were studied with reference to the number of cells; in addition a differentiation of the cells in the blood smear of each case was made by counting 200 cells.

2. A series of normal individuals, and a series of patients with organic heart lesions were used as controls. These were studied in a manner similar to the men with "irritable hearts."

3. The series of functional patients was then analyzed and each type was compared, one with the other. The classification used was based on a study of these patients made by Dr. C. Macfie Campbell.²

* From the Cardiovascular Service, U. S. General Hospital 9.

1. Lewis: Medical Research Committee, Special Report Series 8.

2. Campbell: J. A. M. A. 71:1621, 1918.

4. Special observations on the morphology of the blood following the injection of epinephrin were also carried on in conjunction with the special studies in the reactions to epinephrin, the preliminary report of which has already been published.³ Patients from the Surgical Service, ready for full duty, were used as controls.

5. The type of patient considered "constitutionally inferior" was selected for study to determine his reaction to exercise. Patients with organic heart lesions and those convalescent from rheumatic fever were chosen as controls.

For the differential studies the leukocytes were divided into the following groups:

1. Polymorphonuclear neutrophilic leukocytes (P. M. N.).
2. Polymorphonuclear eosinophilic leukocytes (P. M. E.).
3. Polymorphonuclear basophilic leukocytes (P. M. B.).
4. Lymphocytes, large and small (L. L., S. L.).
5. Mononuclears, large and small (M.).
6. Transitionals (T.).

1 and 2. *Study of General Group of "Irritable Heart" Cases and Controls.*—Two hundred and sixty counts were made on sixty-five patients to determine the number of leukocytes per cubic millimeter of blood. The procedure followed in each case was to have the patient rest for one hour before the blood was taken, and the puncture was made at least two hours after the ingestion of food. The possibility of a variation in the morning and afternoon counts was considered, and each patient was studied with this in mind. Two morning and two afternoon counts were made on each patient on different but not necessarily successive days. With one of the morning counts a blood smear was made by the coverslip method. The pipets were of the Leitz make and each had been checked for error. A Thoma-Levy hemocytometer was used.

Leukocytic Counts:

Average of two a. m. counts on 61 patients.....	8,162
Average of two p. m. counts on 64 patients.....	8,450

Total average day count on 65 patients.....	8,290
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Differential Counts:

Average P. M. N. percentage of 74 patients.....	56.0
Average P. M. E. percentage of 74 patients.....	4.0
Average L. percentage of 74 patients.....	32.6
Small.....	31.0
Large.....	1.7
Average M. and T. percentage of 74 patients.....	7.4

100.0

3. Peabody, et al.: J. A. M. A. 71:1912, 1918.

The results with the controls were as follows:

Leukocytic Counts:

Average of two a. m. counts on 12 organic cases.....	8,460
Average of two p. m. counts on 12 organic cases.....	8,740
Total average day count on 13 organic cases.....	8,400
Average of eight counts on eight normals.....	7,060
Total average count on 21 controls.....	7,900

Differential Counts:

	Thirteen Organics	Eight Normals
Average P. M. N. percentage.....	61.0	60.0
Average P. M. E. per centage.....	1.9	2.6
Average L. percentage:		
S.	26.0	25.0
L.	2.4	2.0
	— 28.1 —	— 27.0 —
Average M. and T. percentage.....	9.0	11.4
	100.0	100.0

TABLE 1.—COMPARISON OF THE LEUKOCYTIC COUNTS IN PATIENTS AND CONTROLS

	Leuko- cytes, Average	Differential Formulas—					
		P. M. N.		P. M. E.		Lymphocytes—	
		Per Cent.	No.	Per Cent.	No.	Per Cent.	No.
"Irritable hearts".....	8,290	56.0	4,642	4.0	332	32.6	2,702
Organic hearts.....	8,400	61.0	5,124	1.9	160	28.1	2,360
Normal controls.....	7,060	60.0	4,236	2.6	184	27.0	1,906
Miller's normal average.....	7,705	63.5	4,895	2.7	218	21.9	1,724

DISCUSSION

The variation in these cases is seen by a comparison of the accompanying tables and charts. There is no appreciable difference in the leukocyte counts of the Organics and the Functionals; in fact, the former show averages slightly above the latter. The normal controls show averages 1,000 cells below either of the series of patients. The averages of Miller⁴ for normals show a less marked difference. It may be concluded that the leukocytes of "irritable heart" patients are slightly increased above the normal, but only to a small degree. In both controls and patients the morning counts average lower than the afternoon, which finding is a normal reaction. The high leukocytosis which Lewis mentioned in his report has not been present in the average of the patients studied in this hospital. The highest count in the "irritable heart" patients was 16,350; the lowest count was 4,700. In the controls the counts varied between 12,300 and 4,500.

From the percentages obtained from counting 200 cells in each smear preparation, the absolute values of the various leukocytes per

4. Miller: Johns Hopkins Bull. 25: 1914.

cubic millimeter of blood were calculated, using as a basis the total day average count. A comparison of the differential results shows that there is a relative lymphocytosis and a decrease in the polymorphonuclear neutrophilic cells in the functional cases. In the controls the figures for the organic cases and the normal individuals are practically the same. The formulas of the controls correspond to the figures determined by Miller.⁴ His figures are tabulated for comparison in Table 1. An eosinophilia was present in all but sixteen patients of this series. The exceptions had a normal percentage. The limits of the eosinophilia ranged from 13 per cent. to 1.5 per cent.

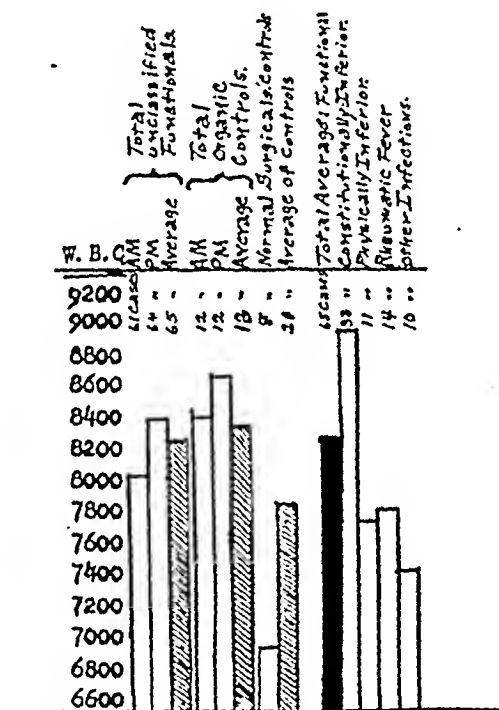


Chart 1.—General comparison of leukocyte counts.

3. *Analysis of the "Irritable Heart" Group.*—The classification used is based on the general suggestions given by Dr. C. Macfie Campbell. Four clinical types have been considered:

1. *Constitutional Inferiority.* This term is used in a very broad sense to cover a very heterogeneous group.

2. *Physical Inferiority.* Separated from the general group of Constitutional Inferiors because of its prominence by numbers among the other types.

3. *Postrheumatic Type.* Soldiers with a definite history of at least one attack of rheumatic fever without discoverable organic findings.

4. *Postinfection Type.* Soldiers convalescing from some infection other than rheumatic fever without organic findings.

The average total counts and the differential formulas of these types are shown in the tables and charts. (Table 2 and Charts 1 and 3.)

TABLE 2.—COMPARATIVE FINDINGS IN THE TYPES OF "IRRITABLE HEART"

Type	Cases		Leukocytes		P. M. N.		P. M. E.		Lymphocytes	
	No.	No.	No.	Per Cent.	No.	Per Cent.	No.	Per Cent.	No.	
Constitutional inferiors..	32	9,000	55.0	4,950	3.8	342	32.0	2,880		
Physical inferiors.....	11	7,800	58.0	4,524	4.0	312	31.6	3,465		
Postrheumatic.....	18	7,900	52.0	4,108	4.0	316	36.5	2,884		
After other infections.....	8	7,500	60.0	4,500	3.7	276	29.0	2,175		

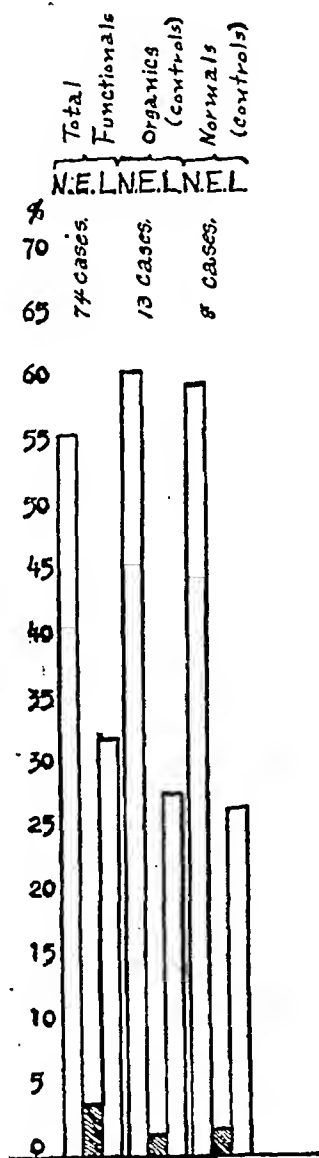


Chart 2.—Comparison of differential counts in "Irritable Hearts," Organic Heart Disease and Normal Controls. N, polymorphonuclear neutrophils; E, polymorphonuclear eosinophils; L, large and small lymphocytes.

In the general Constitutional Inferior Group, the highest leukocytic count was 13,350, and the lowest was 6,000. With the exception of three cases out of a total of thirty-two of this type the white cell count

was above 8,000 cells. The other groups have normal counts. No evidence is found of any direct proportion in leukocyte increase to the severity of the symptoms. In the differential counts the absolute number of cells closely corresponds in all types of the cases.

4. *Studies on the Blood Morphology after Epinephrin Injection.*—The controls used in the blood studies in these observations were

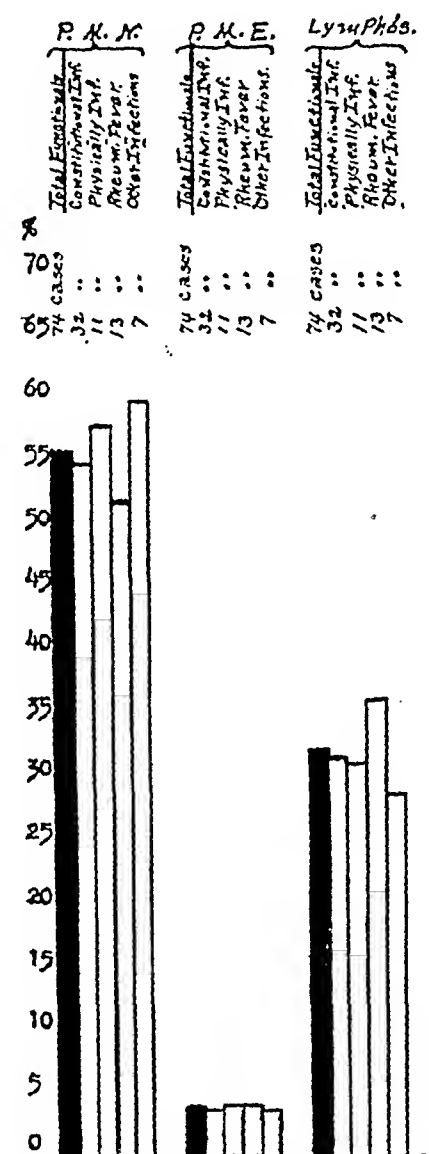


Chart 3.—Comparison of differential counts in four types of "Irritable Hearts."

patients on the Surgical Service, who gave no "effort syndrome" symptoms and gave no reaction after the injection of epinephrin. In each case, with controls and subjects, the patient was placed at rest in bed for one hour previous to the epinephrin injection. At the end of this hour the first specimen of blood was taken. Then 0.5 c.c. of a 1:1,000 solution of epinephrin chlorid was injected intramuscularly. At the height of the reaction in the "epinephrin positive" cases,

and at the end of thirty-five minutes in the negative cases, a second specimen of blood was taken. At the end of an hour, when all the reaction symptoms had subsided, a third specimen was taken. From each of these three specimens leukocytic and differential counts were made. The same pipet was used for each of the three specimens of each individual case in order to avoid any possible error that could be made constant.

TABLE 3.—LEUKOCYTIC COUNTS AFTER EPINEPHRIN INJECTION

	Number Cases	Reaction	After First Hour	At Height of Reaction	After Quiescence
Controls.....	12	Neg.	8,671	11,100	8,425
"Irritable heart".....	16	Pos.	7,812	11,525	8,181

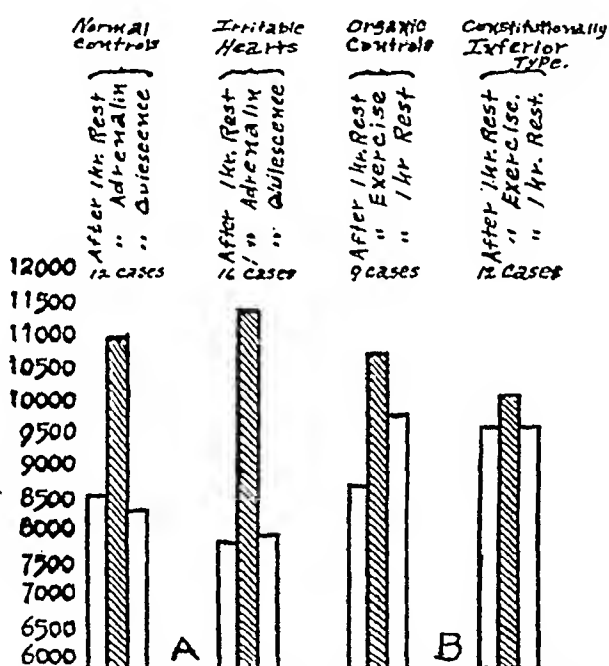


Chart 4.—A. Comparison of leukocytic increase from injection of epinephrin. B. Comparison of leukocytic increase from physical exercise.

TABLE 4.—DIFFERENTIAL STUDIES AFTER EPINEPHRIN

	After Rest				After Epinephrin				After Quiescence			
	P. M. N.		Lymphos.		P. M. N.		Lymphos.		P. M. N.		Lymphos.	
	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
Controls.....	59	5,116	26	2,254	53	5,883	31	3,441	58	4,886	29	2,443
Subjects.....	60	4,687	30	2,344	58	6,684	29	3,342	62	5,072	27	2,209

In both patients having a positive reaction to epinephrin, and in the controls with a negative reaction there was a marked leukocytosis after a period of thirty minutes following the injection of the drug. The percentage of increase in the patients was 47.5, while the percentage in the controls was 28.1. Whether this more marked increase in the patients would also be found in cases of "irritable heart" that do not show a positive reaction to epinephrin has not been determined.

The eosinophil cells were not charted because no variation was found, there being a normal eosinophil count in the controls and a high eosinophilia in the patients before and after the injection of epinephrin.

5. *Blood Morphology in the Type Constitutional Inferior After Exercise.*—A group of patients with organic heart disease was chosen as controls in this study. The subjects were cases of definite "constitutional inferiority." Both controls and subjects were given the same exercises for a period of twenty minutes.

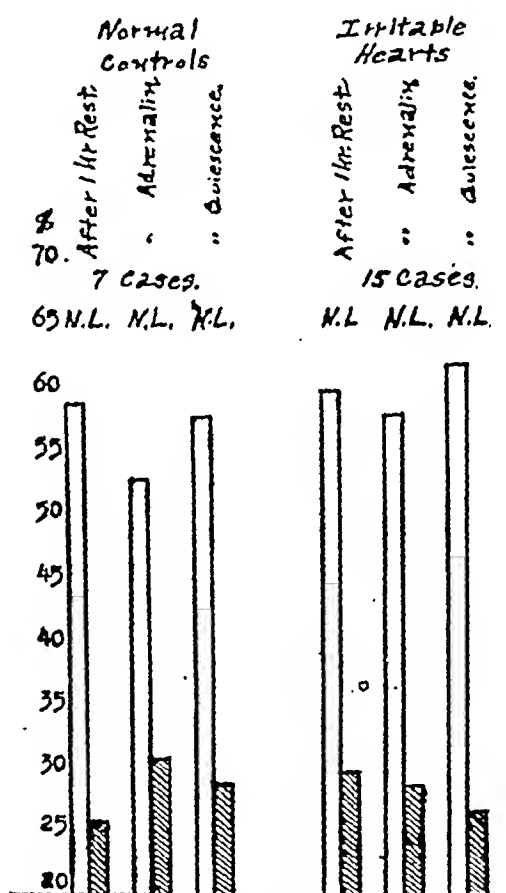


Chart 5.—Comparison of differential counts. Normal Controls, epinephrin negative; Irritable Heart cases, epinephrin positive. Specimens taken at the same time intervals as in Chart 4.

TABLE 5.—LEUKOCYTIC COUNTS BEFORE AND AFTER EXERCISE

	Case Number	After 1 Hour of Rest	After Exercise	After 1 Hour of Rest
Controls.....	9	8,870	10,890	9,960
Subjects.....	12	9,730	10,240	9,740

The subjects show a leukocyte increase of 5.2 per cent. after the exercise, compared with 22.7 per cent. shown by the controls. This difference is explained by the lack of "push" in the inferior type.

They do not make enough effort to cause a normal reaction. Further observations were interrupted by the transfer of the writer to another station.

SUMMARY

1. There is a slight leukocytosis in the unclassified group of patients with "irritable heart." The figures in this correspond, however, to those found in the patients with organic heart disease.

2. The type of patient classed as "Constitutional Inferior" has a high leukocytic count. The other types studied have a normal count.

3. There is a relative lymphocytosis present in the blood of patients with "irritable heart," the limits being between 15 and 51 per cent. An eosinophilia is likewise present, but too much importance cannot be given to this finding, since the presence of parasites was not ruled out.

4. A marked leukocytosis occurs in both patients and controls after the injection of epinephrin. This increase is much greater in the patients with positive reaction than in the controls, who did not respond to the drug.

5. There is no greater variation in the differential formulas after the injection of epinephrin than was to be found before. The eosinophilia persisted in about the same proportion as before.

6. The morphologic studies of the blood in cases of "irritable heart" show nothing of significance that might assist in the diagnosis.

THE INFLUENCE OF FASTING AND VARIOUS DIETS ON THE LIVER INJURY EFFECTED BY CHLOROFORM ANESTHESIA*

PAPER I

N. C. DAVIS AND G. H. WHIPPLE, M.D.

SAN FRANCISCO

As an introduction to a study of liver injury due to chloroform anesthesia, it is necessary to understand clearly how uniform is the individual reaction to this drug under uniform conditions. We submit data in the following papers sufficient to convince a sceptic that the liver injury in a given dog will be uniform in extent provided the intake of food is accurately controlled and the dog is in good clinical condition. The evidence shows that a unit injury due to a unit chloroform anesthesia under fasting conditions will be repeated accurately again and again, provided the dog is given sufficient time to repair each injury to normal. This gives us much confidence in the interpretation of results and enables us to draw finer distinctions in type and extent of injury. In a review of the literature it will be noted that there is the greatest amount of variation in the recorded susceptibility of dogs to chloroform, but little if any data are given to show the *diet conditions* which we feel sure would explain the remarkable discrepancies.

We sometimes record unusual individual resistance or hyper-susceptibility to chloroform poisoning in these experiments, but such exceptions are rare and obtain in all physiologic or pharmacologic experiments. When a sufficient number of experiments are submitted the law of reaction may be established and the few individual exceptions put aside for later consideration. It is truly remarkable to note the uniformity of the liver injury which follows a suitable unit period of chloroform injury given to a dog after three or four days of fasting. Under these conditions the dog is the ideal subject for a study of chloroform injury and repair.

REVIEW OF EXPERIMENTAL WORK

Delayed chloroform injury has been reported occasionally since about 1850, sometimes diagnosed correctly, often called a postoperation acidosis or toxemia of unknown etiology; sometimes called acute yellow atrophy when necropsy material was available. Experimental

*From the George Williams Hooper Foundation for Medical Research, University of California Medical School.

work began in the latter half of the nineteenth century. Strassman,¹ in 1889, determined, among other things, that hemorrhage made dogs more susceptible to injury. In 1905, Bevan and Favill² carefully reviewed the literature, both clinical and experimental, and pointed out that diabetes, hemorrhage, and wasting diseases predispose to injury. In an able article in 1908, Wells³ expressed the belief, postulated by others, that previous liver injury favors a severe chloroform reaction; he also mentioned the fact that sugar feeding is protective against phosphorus poisoning, and presumably would be protective against chloroform injury, also, since the liver can readily use sugar, but protein and fat less easily. He has suggested⁴ that sugar by its antiketonic action tends to maintain cell neutrality, thus preventing acidosis and death. In 1909, Howland and Richards⁵ again reviewed the question of delayed chloroform poisoning, with especial reference to metabolic disturbances. In 1909, Whipple and Sperry⁶ followed experimentally the lesions in various organs, caused by chloroform administration, and gave an excellent histologic picture of the liver injury and repair.

In 1910, Foster⁷ studied the influence of different proportions of protein in the food on resistance to the toxicity of ricin, and on recuperation from hemorrhage. He considered the results with ricin unsatisfactory; and concluded that the resistance to hemorrhage is determined more by breed of dog and individual idiosyncrasies than by total amount of food or amount of protein taken. Hunt⁸ made observations on the effects of a restricted diet and of various diets on resistance of animals to certain poisons, principally acetonitril. Mice or guinea-pigs were used in most experiments. He found that feeding thyroid gland, or blood from cases of hyperthyroidism, conferred a marked resistance to the drugs and decided that other diets had good or bad effects through their influence on the thyroid gland of the recipient. Certain diets, notably dextrose, oatmeal, liver and kidney, greatly increased resistance to acetonitril. Eggs, cheese, milk and various fats greatly lowered resistance. Prostate, ovary and testis acted similarly to, but less markedly than thyroid; thymus, parathyroids and adrenals either had no effect, or one opposite to thyroid. A

1. Strassman: *Virchow's Arch. f. path. Anat.* **115**:1, 1889 (Cited by Bevan and Favill, Footnote 2).

2. Bevan, A. D., and Favill, H. B.: *J. A. M.A.* **45**:691, 1905.

3. Wells, H. G.: *Arch. Int. Med.* **1**:589, 1908.

4. Wells, H. G.: *Chemical Pathology*, Ed. 3, Saunders & Co., 1918.

5. Howland, J., and Richards, A. N.: *J. Exper. M.* **11**:344, 1909.

6. Whipple, G. H., and Sperry, J. A.: *Bull. Johns Hopkins Hosp.* **20**:1, No. 222, 1909.

7. Foster, N. B.: *J. Biol. Chem.*, **7**:379, 1910.

8. Hunt, Reid: *Hyg. Lab. Bull.*, 1910, No. 69.

restricted diet usually gave more resistance than either overfeeding or starvation.

Whipple⁹ found that pups, during the first three weeks of life, are very insusceptible to chloroform injury, and suggested a correlation between this phenomenon and the presence in these young animals of persisting cell nests of blood-forming elements, although it was not known what neutralizing action they could exert. Mosiman and Whipple¹⁰ also found that the pigeon, frog and terrapin are extremely resistant to chloroform. It is interesting that these animals have nucleated red blood corpuscles. Graham¹¹ has maintained that the resistance of pups is due to the high content of glycogen in their livers, and obtained the typical injury after a short preliminary starvation, or starvation and phlorizin. Adult animals were also rendered more resistant by preliminary sugar feeding. A similar explanation has not been offered for the insusceptibility of birds, reptiles and amphibians. Nutritional analyses¹² show a carbohydrate content in the livers of the chicken, turkey and goose, which is quite comparable to that in mammalian livers.

In 1914-1915 Opie and Alford¹³ published articles on the influence of diet on the hepatic lesions of chloroform, phosphorus or alcohol, and on the nephritis caused by potassium chromate, uranium nitrate or chloroform. Rats were used as experimental animals; chloroform was given subcutaneously. Susceptibility to all poisons was found to be less after a rich carbohydrate diet. The toxicity of chloroform and uranium nitrate was greatest after a fat diet; that of phosphorus was greatest after a meat diet. Brain and egg yolk, containing lecithin, cholesterol, etc., apparently predisposed to injury similarly to fat. Fat mixtures were less efficacious as diets than the combinations minus fat. The conclusion was drawn that the great solubility of fat in chloroform, and the relative fixation of chloroform by the body fat and watery fluids, determines the increased susceptibility of animals which have received fat and stored it in the parenchymatous cells of the liver and kidney; factors of location must not be overlooked, since all fatty tissues are not necrotized.

McDanell and Underhill¹⁴ have shown that in rabbits a base-forming diet, such as carrots, is somewhat more efficient than an acid-forming diet, such as oats, in the formation of liver glycogen. Early

9. Whipple, G. H.: *J. Exper. M.* **15**:359, 1912.

10. Mosiman, R. E., and Whipple, G. H.: *Bull. Johns Hopkins Hosp.* **23**:1, No. 261, 1912.

11. Graham, E. A.: *J. Exper. M.* **21**:185, 1915.

12. *Bull. 28 (Revised), Office of Experiment Stations.*

13. Opie, E. L., and Alford, L. B.: *J. A. M. A.* **62**:895, 1914; *J. Exper. M.* **21**:1, 1915.

14. McDanell, L., and Underhill, F. P.: *J. Biol. Chem.* **29**:255, 1917.

in 1918 Salant and Swanson¹⁵ published their observations on the influence of diet on the toxicity of sodium tartrate, and on the nephritis caused by sodium tartrate, as measured by renal function tests. Cats, rabbits and rats were used as experimental animals. In cats a decreased resistance was found with starvation, and with meat feeding. Carbonates increased resistance, perhaps by a relief of acidosis caused by organic acids. Resistance of rabbits was the same on starvation, and on acid or alkaline diet. Toxicity of sodium tartrate was greatest on a diet of oats, hay and cabbage. Diets rich in sugar were efficacious in decreasing toxicity, the most pronounced being carrots; carrot leaves were also good. It was suggested that the favorable effect may be due to several factors, such as: inhibition of bacterial activity in the intestines; vitamins; or other unknown constituents of the diet.

Very recently Simonds¹⁶ has reported that sugar feeding to normal animals seems to have no effect on the ereptic power of organs, but feeding sugar before and after phosphorus poisoning apparently prevents the reduction of the ereptic power of the liver, which usually takes place after phosphorus injection.

The picture of chloroform injury, described by so many workers, seems to depend, therefore, not only on the amount of chloroform administered, but on the subject's previous nutrition as well. The milder injuries usually cause more or less fatty change in the liver; the more intense injuries produce actual necrosis. The typical chloroform necrosis affects the centers of the liver lobules, showing from six to ten hours after administration of the drug. The dead area usually appears hyaline, and quite homogeneous for from twenty-four to forty-eight hours. Wandering cells then make their appearance and aid the tissue ferments in removing the necrotic mass between the second and fifth days, in cases of recovery. During the process of dissolution the neighboring, intact liver cells begin to proliferate; mitoses become numerous; cell strands extend in to occupy the stroma recently filled by dead material. Even under favorable conditions there is usually a period between the removal of debris, and final repair, when a certain amount of collapse of unfilled stroma is to be seen surrounding the central veins.

Taylor,¹⁷ and later, Wells,¹⁸ have shown by chemical analyses of livers from fatal, human cases of chloroform poisoning, that there is a high amino-acid and fat content.

15. Salant, W., and Swanson, A. M.: *J. Pharm. and Exper. Therap.* **11**:43, 1918.

16. Simonds, J. P.: *J. Exper. M.* **28**:673, 1918.

17. Taylor, A. E.: *Univ. Calif. Pub. (Pathol.)*, **1**:43, 1904.

18. Wells, H. G.: *J. Biol. Chem.* **5**:129, 1908-1909.

In this communication we are presenting the results of some feeding experiments corroboratory of Opie's work on rats, which bring out a few new and interesting points.

METHODS

Young dogs and pups were used, principally, as experimental animals; a few older, adult, dogs were utilized; rats, also, were used in some experiments. Feeding of special diets usually lasted from three to six days, the exact time being indicated in the individual protocols. Data has accumulated on numerous starvation controls, but to avoid repetition only a limited number of these records are indicated in our tables. In most cases food has been left in the cages for the dogs; pups eat special or limited diets more readily than the older dogs. Fluids, such as cottonseed oil, sugar solution, beef extract solution, etc., have been given by stomach tube.

Dogs have been anesthetized with chloroform (either Squibb's, or Powers-Weightman-Rosengarten Co.'s U. S. P. products) by the drop method for definite time intervals; rats have been chloroformed in groups in an improvised gas chamber; a relatively light anesthesia has been deemed sufficient in all cases. Pups have been anesthetized for one hour; older dogs which were starved only three days have usually been given one and one-half hours, those starved four days being given one and one-fourth hours. Young dogs show a more uniform reaction under standard conditions than do old dogs.

Operations have always been performed under ether anesthesia, with all aseptic precautions. This has not always prevented postoperative infection. Moreover, it has often seemed that the operative wounds have a tendency to open superficially because of imperfect reparative processes, associated with the limited diets. The operative procedure itself is very simple. A laparotomy is done and either a tip of one of the projecting smaller lobes is ligatured and snipped off, or a mattress suture is put in one of the larger lobes a short distance from the margin, tightened, and a small wedge of tissue removed from the area where the blood supply is shut off. Fixation has been in formaldehyd solution; material has been divided for frozen sections, with fat staining, and for imbedding, with later hemotoxylin and eosin staining.

In cases in which animals have been sacrificed, ether anesthesia has been used, and death accomplished by exsanguination. In such cases sections have been procured from other organs besides the liver.

There may be a criticism that a section from the edge of the liver does not fairly indicate the injury toward the center of the lobe, or in other lobes. It is true that the liver parenchyma underlying the capsule does show a more severe injury than an equal strip through the center of a lobe; however, this layer is very thin, and even in the smallest sections which we have removed it is always possible to find many lobules which are fair representatives of the interior. With necropsy material it has always been our custom to obtain sections from various locations, and these always present practically the same picture. When dogs die a few hours after operation, the operative and necropsy material invariably show the same amount of injury.

It may be noted that in certain instances we have used the same dog for several experiments. We have found, as did Opie, Barker and Dochez,¹⁹ that dogs which survive an initial chloroform injury may be given chloroform thereafter on successive or alternate days for a week

19. Opie, F. L., Barker, B. I., and Dochez, A. R.: *J. Exper. M.* **13**:162, 1911.

or two without increasing the original necrosis, although the liver may become intensely fatty and the animal very much jaundiced and intoxicated. Quinan²⁰ also mentions this phenomenon of chloroform tolerance. If the dog is allowed to recover for two or three weeks, however, a tolerance to a second dose is not exhibited. As has been already mentioned, Wells and others have thought that a previous liver injury is a predisposing factor in subsequent chloroform injuries. We have found no indication of such action in our dogs. While we have tabulated no experiments to prove, or disprove, this point, a perusal of the experiments in this and the following papers will indicate that successive injuries following equal doses of chloroform are comparable, other factors being equal.

EXPERIMENTAL OBSERVATIONS

Table 1 briefly presents the results of a number of feeding experiments with carbohydrates, fat alone, and mixtures containing a considerable amount of fat as one constituent. Representative protocols of experiments here tabulated immediately follow.

TABLE 1.—CARBOHYDRATE FEEDING; STARVATION; FAT FEEDING

Experiment	Diet	Chloroform	Liver Injury		Remarks
			Central Necrosis	Fat	
1 (Pup 3c)	Carbohydrate (sugar, rice, potatoes, etc.)	1 hr.	0	1/3; slight and diffuse	Blood urea low
2 (Pup 4e)	Carbohydrate (sugar, rice, potatoes, etc.)	1 hr.	0	2/3; scattered	
3 (Adult 19-34)	100 gm. sugar daily; 5 days	1¼ hr.	1/2-3/5	1/3; heavy	
	Starvation 4 days (control)	1¼ hr.	3/4	Heavy to periphery	Operated on; hemorrhage uncontrollable; hemorrhage + liver injury fatal
4 (Pup 3b)	Starvation 4 days (control)	1 hr.	4/5	Moderate throughout	Fatal injury
5 (Pup 3e)	Fat (butter, lard, fat meat)	1 hr.	1/3	4/5; heavy	
6 (Pup 4b)	Fat (butter, lard, fat meat)	1 hr.	3/4	Heavy to periphery	Fatal injury; fibrin low; blood urea very high; calcium deposits in liver
7 (Pup 4e)	Fat and carbohydrate (lard, butter, fat meat, rice and potatoes)	1 hr.	1/2	1/2; heavy zone about necrosis	Blood urea very high
8 (Pup 5e)	Fat and carbohydrate (lard, butter, fat meat, rice and potatoes)	1 hr.	3/4	Heavy to periphery	Blood urea high
9 (Pup 19-56)	Skeletal muscle and fat	1 hr.	1/2	1/3; moderate	

EXPERIMENT 2.—*Carbohydrate Diet*.—Pup 4 c, a black female mongrel.

May 23: Isolated; starvation; pup is 2 or 3 months old; bright and active.

May 24: Wt., 5.88 lbs. Feeding begun; food consists of potatoes, rice, cracker meal and sugar, *ad lib.*; eaten well.

May 25: Wt., 5.96 lbs. Food eaten well.

May 26: Wt., 5.88 lbs. Food eaten well.

May 27: Wt., 5.7 lbs. *Chloroform for 1 hour* (from 9:40 to 10:40 a. m.).

May 28: Wt., 5.5 lbs. Eats very little; continues active.

May 29: Wt., 5.25 lbs. Sacrificed in a. m.; blood urea, 25 mg.; urea N., 12 mg.; fibrin, 260 mg. per 100 c.c. plasma.

Necropsy Report.—Blood does not clot quite as readily as normal. Liver: Weight, 74 gm.; no necrosis apparent; looks fatty, however; remaining viscera negative.

Microscopic Report.—Liver: No necrosis; central two thirds of each lobule contains a small amount of diffuse fat in very small droplets.

EXPERIMENT 3.—*Sugar Diet*.—Dog 19-34; adult, brown and white male terrier.

Oct. 10: Wt. 16.6 lbs. Isolated; recovering from distemper; one eye still sore; very active; sugar by stomach tube: 75 gm. cane sugar, 25 gm. glucose, and kaolin.

Oct. 11: Wt. 16.38 lbs.; Oct. 12, Wt., 16.13 lbs.; Oct. 13, Wt., 15.75 lbs.; dog continues active; 100 gm. sugar daily.

Oct. 14: Wt., 15.75 lbs. Sugar in a. m. *Chloroform for one and a quarter hours* (from 2 to 3:15 p. m.).

Oct. 15: Wt., 15.2 lbs. Bright and active; no food.

Oct. 16: Wt., 14.8 lbs. Bright and active; no food. *Piece of liver removed* at 4 p. m.; necrosis one half to three fifths; fat ++.

Oct. 17: Full diet; mixed food.

Oct. 19: Eats all right; distemper entirely gone; wound satisfactory.

EXPERIMENT 3.—*Starvation (Control)*.—Dog 19-34 (continued).

Oct. 28: Wt., 16.25 lbs. Isolated for starvation (before daily feeding); active and in good condition; wound practically all healed.

Oct. 29: Wt., 15.5 lbs.; Oct. 30, Wt., 15.25 lbs.; continues active; no food.

Oct. 31: Wt., 14.7 lbs. Lively and in good condition. *Chloroform for one and a quarter hours* (from 1:10 to 2:25 p. m.).

Nov. 1: Wt., 14.3 lbs. Still very active.

Nov. 2: Wt., 14.13 lbs. Active. *Piece of liver removed* at 10:30; excessive bleeding.

Nov. 3: Found dead.

Necropsy Report.—Much free blood in peritoneal cavity; liver shows no normal tissue; extensive necrosis and fat; duodenum injected.

Microscopic Report.—Liver shows three fourths or more necrosis; remainder fatty. There seems to be a slight removal of debris between operation and death. *Kidneys*: cloudy swelling. *Spleen*: hemorrhage.

EXPERIMENT 4.—*Starvation (Control)*.—Pup 3 b, a black female mongrel.

May 14: Isolated. This pup was chosen for starvation because the heaviest in the litter, and in excellent condition.

May 15: Wt., 6.25 lbs.; May 16, Wt., 6 lbs.; May 17, Wt. 5.7 lbs.; no food.

May 18: Wt., 5.56 lbs. *Chloroform for one hour* (from 10:30 to 11:30 a. m.); no food.

May 19: Wt., 5.2 lbs. The pup was noisy but lively even after chloroform; no food.

May 20: Wt., 5.06 lbs. Found dead.

Necropsy Report.—Blood is not clotted, and refuses to clot on contact with tissues (autolysis?). *Thymus*: shows many ecchymoses. *Lungs*: one dark area (probably hypostasis) in left lower lobe. *Liver*: weight, 109 gm. The lobule centers are large and dark and are surrounded by light opaque zone extending almost to the peripheries, leaving very little normal, translucent tissue. *Duodenal mucosa*: slightly injected; no hemorrhages.

Microscopic Report.—*Thymus*: congestion and some hemorrhage. *Lungs*: congestion; no hemorrhage. *Liver*: about four fifths necrotic. Fat ++. *Kidneys*: slight cloudy swelling.

EXPERIMENT 6.—*Fat Diet.*—Pup 4 b, a brindle male.

May 23: Isolated; starvation; pup is 10 weeks old; bright and active.

May 24: Wt., 6 lbs. Feeding begun; diet consists of lard, butter and bits of fat from garbage can, mixed with a very little cracker meal.

May 25: Wt., 6.38 lbs.; May 26, Wt., 6.3 lbs.; fat eaten with a good appetite.

May 27: Wt., 6.25 lbs. Chloroform for one hour (from 10:50 to 11:50 a. m.).

May 28: Wt., 5.8 lbs. No food touched since anesthesia; sick; very thirsty; vomits; sacrificed at 4 p. m.; blood urea, 101 mg.; urea N., 47 mg.; fibrin, 94 mg. per 100 c.c. plasma.

Necropsy Report.—Blood not clotted after a half hour contact with tissues. *Liver*: weight, 148 gm. Lobules about four fifths a dull pink; opaque and yellow to peripheries. *Spleen*: mottled brown and purple; malpighian bodies very large and milky.

Microscopic Report.—*Liver*: about three fourths necrosis, totally unresolved; almost all of remaining cells are extensively vacuolated with fat; fat also extends into necrotic area; some masses in the necrosis suggest calcium deposits. *Kidneys*: a little cloudy swelling. *Spleen*: hyperemic.

EXPERIMENT 8.—*Fat and Carbohydrate Diet.*—Pup 5c, a black spaniel, male.

June 3: Isolated; starvation; pup is 6 weeks old; healthy and active.

June 5: Wt., 6.25 lbs. Feeding begun; fat and carbohydrate in approximately equal parts; fat= butter, lard and bits of fat meat from garbage. Carbohydrate= rice and potatoes. Food *ad lib*.

June 6: Wt., 6.13 lbs. Food same as yesterday; does not eat very much.

June 7: Wt., 6 lbs. Added 30 c.c. cottonseed oil and 30 gm. sugar to diet.

June 8: Wt., 5.96 lbs. Sugar and oil as yesterday (by stomach tube). Chloroform for one hour (from 10:25 to 11:25 a. m.).

June 9: Wt., 5.56 lbs. Sugar and oil again; vomited.

June 10: Wt., 5.63 lbs. Quite sick; sacrificed in a. m.; blood urea, 81 mg.; urea N., 38 mg.; fibrin, 140 mg. per 100 c.c. plasma.

Necropsy Report.—*Liver*: weight, 116 gm. Gross appearance of about one half necrosis, and fat practically to periphery of lobules.

Microscopic Report.—*Liver*: about three fourths necrosis; all more or less fatty. *Kidneys*: slight congestion and cloudy swelling.

EXPERIMENT 9.—*Fat and Lean Meat Diet.*—Dog 19-56, a female, collie pup.

Nov. 3: Wt., 7.06 lbs. Isolated for feeding; previously given beef extract, then chloroform and regeneration on kidney diet; wounds in good shape. 100 gm. skeletal muscle + 100 gm. fat from beef hearts.

Nov. 4: Wt., 6.8 lbs. Ate some of yesterday's food; 75 gm. meat + 75 gm. lard.

Nov. 5: Wt., 6.8 lbs.; Nov. 6, Wt., 7.13 lbs.; 75 gm. meat + 75 gm. lard daily; eats well.

Nov. 7: Wt., 6.8 lbs. Fat and meat. Chloroform for one hour (from 3:05 to 4:05 p. m.).

Nov. 8: Wt., 6.75 lbs. Mixed food. Eats some. Rather quiet.

Nov. 9: Wt., 6.56 lbs. Sacrificed at 11 a. m.

Necropsy Report: Liver is pale, yellowish, opaque—probably fatty throughout—with distinct lobule centers, representing undoubted necrosis of one third or more. Other organs negative.

Microscopic Report: Liver: about one half necrotic; fat ++. Spleen: malpighian bodies enormous.

Experiments 1 and 2 illustrate very well the resistance to chloroform exhibited by pups previously fed a carbohydrate diet. The contrast between the injury sustained by these pups and by the control on starvation (Experiment 4) is very striking. Experiment 3 may appear atypical, but it must be realized that this was an adult dog receiving only 100 gm. of sugar daily, and that this amount lessened the injury which might have been expected (compare control) and undoubtedly saved the animal's life in the first instance. Apparently, the dog was very susceptible to chloroform injury. It will be observed that in Experiments 5 to 9, where fat is a feature of the diet, the injury conforms to the type obtained after starvation. There seems to be a slight resistance in some cases, but, in general, it must be concluded that fats, and food combinations containing fat in large amounts are not protective. Furthermore, when it is considered that large amounts of protective carbohydrate fail to prevent the bad effect of the fat quota in a mixture, it would appear that a negative value should be attached to fats; that is, they are not only not protective against chloroform injury, but are actually harmful. These results corroborate the work of Opie on rats. It may be mentioned that we have also found that rats fed on fat are very susceptible to chloroform injury.

TABLE 2.—FEEDING OF BRAIN AND PARENCHYMATOUS ORGANS

Experiment	Diet	Chloroform	Liver Injury		Remarks
			Central Necrosis	Fat	
10 (Pup 19-44)	Brain and cracker meal	1 hr.	0	0	
11 (Pup 19-41)	Brain	1 hr.	Trace	0	Died from distemper a few hours after chloroform; hardly time for necrosis to show well
12 (Pup 19-81)	Brain	1 hr.	0	0	
13 (Pup 19-88)	Brain	1 hr.	Trace	0	A few focal necroses
14 (Pup 19-43)	Kidney	1 hr.	0	0	
15 (Pup 5d)	Liver	1 hr.	Trace	3/4; intense in central 1/3	
16 (Pup 3f)	Liver	1 hr.	0	Trace	Blood urea very high; fibrin high

EXPERIMENT 12.—*Brain Diet*.—Dog 19-81, a female Airdale pup.

Nov. 27: Wt., 11.9 lbs. Isolated for feeding; very active; skinny; 400 gm. *brain*.

Nov. 28: Wt., 11.3 lbs.; 400 gm. *brain*; all eaten.

Nov. 29: Wt., 10.75 lbs.; Nov. 30, Wt., 10.63 lbs.; Dec. 1, Wt., 10.44 lbs.; Dec. 2, Wt., 10.25 lbs.; 500 gm. *brain* daily; all eaten.

Dec. 3: Wt., 10.2 lbs.; 250 gm. *brain*; active. Chloroform for one hour (from 9:45 to 10:45 a. m.).

Dec. 4: Wt., 10.13 lbs. Casein diet.

Dec. 5: Wt., 9.9 lbs. Casein diet. *Piece of liver removed at 3:30*. No fat; no necrosis; lobule centers stain lightly; cytoplasm is somewhat granular, etc.

Dec. 6: Wt., 9.9 lbs. Experiment discontinued; mixed food.

EXPERIMENT 13.—*Brain Diet*.—Dog 19-88, a female coach puppy.

Dec. 23: Wt., 5.75 lbs. Isolated; mean-tempered; no food for twenty-four hours; in fair condition; *brain ad lib.*; does not eat very much.

Dec. 24: Wt., 5.63 lbs.; Dec. 25-27, *brain ad lib.*; eats about 150 gm. daily.

Dec. 28: Wt., 5 lbs. *Chloroform for one hour* (from 10:55 to 11:55 a. m.).

Dec. 29: Wt., 5.06 lbs. Active; meat diet.

Dec. 30: Wt., 5 lbs. Active; meat diet. *Piece of liver removed at 2:15*. Sections show *no fat*; very little central necrosis. The central two thirds of each lobule takes a light stain, is granular, slightly vacuolated, etc.; a few focal necroses.

Dec. 31: Developing distemper; experiment discontinued.

Jan. 5: Found dead; distemper pneumonia.

EXPERIMENT 14.—*Kidney Diet*.—Dog 19-43, a black, mongrel, female pup.

Oct. 3: Wt., 5.7 lbs. Isolated for feeding; about 10 weeks old; pup has mange and many fleas, but is active and very noisy; gave 100 gm. of *ground kidney*.

Oct. 4: Wt., 5.3 lbs.; 130 gm. *kidney*; Oct. 5, Wt., 5.25 lbs.; 140 gm. *kidney*.

Oct. 6: Wt., 5.2 lbs.; 150 gm. *kidney*.

Oct. 7: Wt., 5.13 lbs.; 150 gm. *kidney*. *Chloroform for one hour* (from 11:20 to 12:20).

Oct. 8: Wt., 5 lbs.; 100 gm. *kidney*; apparently not sick.

Oct. 9: Wt., 5 lbs.; 150 gm. *kidney*. *Piece of liver removed in p. m.*; frozen sections show practically no liver injury. Experiment discontinued.

EXPERIMENT 15.—*Liver Diet*.—Pup 5 d, a black spaniel, female.

June 3: Isolated; starvation; pup is 6 weeks old; healthy and active.

June 5: Wt., 5.7 lbs. Feeding begun; *ground liver ad lib.*

June 6: Wt., 5.63 lbs.; June 7, Wt., 5.44 lbs.; *liver ad lib.*; eats fairly well.

June 8: Wt., 5.56 lbs. *Chloroform for one hour* (from 9:15 to 10:15 a. m.).

June 9: Wt., 5.5 lbs. Remains well and active; *liver diet* continued.

June 10: Wt., 5.4 lbs. Sacrificed in a. m.; blood urea, 48 mg.; urea N., 22.5 mg.; fibrin, 275 mg. per 100 c.c. plasma.

Necropsy Report.—Liver weight, 96 gm.; no necrosis apparent; fat quite extensive—over about three fourths of each lobule.

Microscopic Report.—*Liver*: three fourths fatty, quite intense in central one third; no necrosis.

EXPERIMENT 16.—*Liver Diet*.—Pup 3 f, a black and white female mongrel.

May 14: Isolated; starvation; bright and active.

May 15: Wt., 5.56 lbs. Feeding begun; *ground liver ad lib.*

May 16: Wt., 5.5 lbs.; May 17, Wt., 5.11 lbs. *Liver* eaten well.

May 18: Wt., 5.5 lbs. *Chloroform for one hour* (from 10:30 to 11:30 a. m.).

May 19: Wt., 5.4 lbs. Eats very little.

May 20: Wt., 4.9 lbs. Sacrificed in p. m.; blood urea, 104 mg.; urea N., 48 mg.; fibrin, 800 mg. per 100 c.c. plasma.

Necropsy Report.—Blood definitely anemic. *Liver:* Wt., 110 gm.; tissue is not uniform; some portions are grayer than others; lobule centers are rather prominent; fat probably present. *Kidneys* show numerous subcapsular petechiae; cortices pale. *Stomach* contains pieces of excelsior.

Microscopic Report.—*Liver:* Slight amount of diffuse fat in neighborhood of central veins; no central necrosis; a few small lymphocytic cell nests. *Kidneys:* Quite severe hyaline necrosis in convoluted tubules; some casts yellow in color; much cell infiltration, more diffuse than in the pyelonephritis of the other pups.

Experiments 10 to 13 illustrate a decided resistance to injury afforded by feeding brain previous to chloroform anesthesia. This result was a decided surprise to us. The work of Hunt on acetonitril, using mice as experimental animals, and the work of Opie on chloroform and other drugs, using rats as experimental animals, seemed to place brain in the same class as fats, presumably on account of its lipoidal content (lecithin, cholesterol, etc.). It would appear from these experiments, however, that brain feeding does not predispose to chloroform injury in dogs.

Experiments 14, 15 and 16 demonstrate a protective value for the parenchymatous organs, liver and kidney. Such an action by these foods was also noted by Hunt, against the effects of acetonitril. Our observations on rats seem to indicate that liver diet is less uniformly protective for them than it is for dogs.

TABLE 3.—FEEDING OF SKELETAL MUSCLE, BEEF HEART AND BEEF EXTRACT

Experiment	Diet	Chloroform	Liver Injury		Remarks
			Central Necrosis	Fat	
17 (Pup 3d)	Skeletal muscle	1 hr.	1/5	2/3; heavy zone about necrosis	Blood urea high
18 (Pup 4f)	Skeletal muscle	1 hr.	Trace	4/5; scattered	Fibrin high
19 (Pup 5e)	Skeletal muscle	1 hr.	1/2-3/5	Heavy to periphery	
20 (Pup 5b)	Beef heart	1 hr.	1/2	1/2; heavy zone about necrosis	Fibrin low
21 (Pup 19-56)	5 gm. beef extract daily for 4 days	1 hr.	Trace	1/2; heavy	Severe cytoplasmic injury without definite necrosis
22 (Adult 19-61)	10 gm. beef extract daily for 5 days	1 1/4 hr.	1/3-2/5	1/3; scattered	Cytoplasmic injury up to 1/2

EXPERIMENT 18.—*Lean Meat Diet.*—Pup 4 f, black female mongrel.

May 23: Isolated; starvation; pup is 2 or 3 months old; bright and active.

May 24: Wt., 3.38 lbs. Feeding begun; *ground skeletal muscle ad lib.*

May 25: Wt., 3.5 lbs.; May 26, Wt. 3.3 lbs.; eats well; *meat ad lib.*

May 27: Wt., 3.38 lbs. *Chloroform for one hour* (from 9:40 to 10:40 a. m.).

May 28: Wt., 3.25 lbs. Continues active; appetite good.

May 29: Wt., 3.25 lbs. Sacrificed in a. m.; blood urea, 39 mg.; urea N., 18 mg.; fibrin, 554 mg. per 100 c.c. plasma.

Necropsy Report.—Blood clots very well. *Liver:* Wt., 56 gm. No central congestion; fat, if present, must be in small amount and diffuse; other organs negative.

Microscopic Report.—*Liver:* A few necrotic cells; cloudy swelling; fat over most of tissue, considerable in amount, but very finely divided. *Kidneys:* Somewhat diffuse, chronic pyelonephritis.

EXPERIMENT 19.—*Lean Meat Diet.*—Pup 5 e, a black spaniel, male.

June 3: Isolated; starvation; pup is 6 weeks old; healthy and active

June 5: Wt., 4.38 lbs. Feeding begun; *ground skeletal muscle ad lib.*

June 6: Wt., 4.25 lbs.; June 7, Wt., 4.2 lbs.; *meat ad lib.*; eats well.

June 8: Wt., 4.2 lbs. *Chloroform for one hour* (from 9:15 to 10:15 a. m.); *meat diet.*

June 9: Wt., 4.13 lbs. Continues lively; *meat diet.*

June 10: Wt., 4.13 lbs. Sacrificed in a. m.; blood urea, 48 mg.; urea N., 22.5 mg.; fibrin, 145 mg. per 100 c.c. plasma.

Necropsy Report.—*Liver:* Weight, 77 gm.; central areas are red and typical of necrosis; lobules opaque almost to peripheries; other organs negative.

Microscopic Report.—*Liver:* Necrosis of one half to three fifths, surrounded by intense zone of fat to periphery in each lobule.

EXPERIMENT 20.—*Beef Heart Diet.*—Pup 5 b, a brown spaniel, male.

June 3: Isolated; starvation; pup is 6 weeks old; healthy and active.

June 5: Wt., 6.06 lbs. Feeding begun; *ground beef heart ad lib.*

June 6: Wt., 6.06 lbs.; June 7, Wt., 5.15 lbs.; *beef heart ad lib.*; eats fairly well.

June 8: Wt., 5.88 lbs. *Chloroform for one hour* (from 9:15 to 10:15 a. m.).

June 9: Wt., 5.8 lbs. Apparently in good condition.

June 10: Wt., 5.63 lbs. Sacrificed in a. m.; blood urea, 41 mg.; urea N., 19 mg.; fibrin, 70 mg. per 100 c.c. plasma.

Necropsy Report.—*Liver:* Weight, 120 gm.; lobule centers very red and distinct; opaque with fat almost to peripheries; other organs negative.

Microscopic Report.—*Liver:* about one half frank necrosis, surrounded by a zone of intense fat, and slight diffuse fat in the remainder. *Kidneys:* slight cloudy swelling.

EXPERIMENT 21.—*Beef Extract Diet.*—Dog 19-56, a female collie pup.

Oct. 12: Wt., 7.56 lbs. Isolated for feeding; pup is probably 2 or 3 months old; lean and active; 5 gm. *beef extract* + salt and kaolin in 150 c.c. water, by stomach tube.

Oct. 13: Wt., 7.13 lbs.; Oct. 14, Wt., 7.0 lbs.; 5 gm. *beef extract* daily.

Oct. 15: Wt., 6.7 lbs.; 4 gm. *beef extract.*

Oct. 16: Wt., 6.63 lbs. *Chloroform for one hour* (from 10:30 to 11:30 a. m.); 150 gm. kidney in p. m.

Oct. 17: Wt., 6.75 lbs. A little dull; 150 gm. kidney.

Oct. 18: Wt., 6.8 lbs.; 150 gm. kidney.

Piece of liver removed at 3 o'clock. Almost died under anesthetic. Sections show very little frank necrosis, but a rather severe cytoplasmic injury—large vacuolated liver cells, with heavy deposits of fat over one half of each lobule; wandering cells present.

Regenerated on kidney diet.

EXPERIMENT 22.—*Beef Extract Diet.*—Dog 19-61, a black spaniel, female adult.

Nov. 5 Wt., 23.13 lbs. Isolated before daily feeding; active and in good condition; 10 gm. *beef extract* + kaolin in 100 c.c. water by stomach tube.

Nov. 6 Wt., 22.7 lbs.; Nov. 7, Wt. 22.25 lbs.; Nov. 8, Wt., 21.75 lbs.; 10 gm. beef extract daily.

Nov. 9 Wt., 21.56 lbs.; 10 gm. beef extract. Chloroform for one and one fourth hours (from 9.45 to 11 a. m.).

Nov. 10: Wt., 21.06 lbs.; sore eye, and sneezes (distemper?); casein diet.

Nov. 11 Wt., 20.9 lbs. Casein diet; vomited; operation at 3 o'clock; died under anesthetic.

Necropsy Report: Organs all congested; subendocardial hemorrhages. *Liver:* Marked dimpling and probable necrosis; fat not apparent. *Kidneys:* Cortices somewhat swollen and opaque.

Microscopic Report.—*Liver:* Necrosis one third to two fifths; engorgement; pigmentation; fat one third, scattered. *Spleen* contains pigment.

Experiments 17 to 19 are illustrative of effects obtained from feeding lean meat to dogs previous to chloroform anesthesia. The three experiments are in themselves somewhat discordant, but an average is suggestive of a certain degree of liver protection. At least, the injury obtained is far less than that usually resulting after fat feeding and chloroform. It appears, however, that the protective action of meat feeding is inferior to that of carbohydrate feeding. Experiment 9, in Table 1, should be compared with the experiments on meat feeding alone. It will be noted that the addition of fat to meat intensifies the action of chloroform on the liver in an average case. It will be observed that these cases conform to Opie's conclusions regarding the chloroform injury in rats after meat feeding. It will be recalled that Opie found a more intense phosphorus injury after meat feeding than after fat feeding; and Salant and Swanson found that cats were rendered susceptible to injury from sodium tartrate after a meat diet.

Beef heart is tabulated with lean meat because its dietary action is more like that of muscular tissue than that of the parenchymatous organs. Experiments 21 and 22 show a rather interesting protection afforded by a diet of beef extract. This protection is entirely out of proportion to the very small amount of food concerned. For instance, Experiment 22 shows a moderate injury, but this is in an adult dog, and if starved five days and given an hour and a quarter chloroform anesthesia, he might be expected to show approximately twice the necrosis actually found.

EXPERIMENT 23.—*Thyroid Feeding Previous to Chloroform.*—Dog 18-124, a young black and white female.

Aug. 19: Wt., 14.7 lbs. Isolated; rather lean; gave 3 gm. thyroid powder in 200 c.c. water in a. m.; vomited; brought up two round worms; salivated. P. M.: Gave 3 gm. more thyroid; partly retained; left $\frac{1}{2}$ gm. thyroid in a little damp cracker meal in cage; gave 10 drops oil of chenopodium in alcohol.

Aug. 20: Wt., 13.9 lbs. Small amount of feces and many worms in cage; bright and active; 3 gm. thyroid retained; $\frac{1}{2}$ gm. left in cage yesterday was eaten later.

Aug. 21: Wt., 12.94 lbs.; 3 gm. thyroid retained.

Aug. 22: Wt., 12.63 lbs.; 3 gm. thyroid in a. m. Chloroform for one and one-fourth hours (from 2:25 to 3:40 p. m.).

Aug. 23: Wt., 13.0 lbs. Active; diet of sugar and potatoes.

Aug. 24: Wt., 12.5 lbs. Bright and active; left potatoes in cage. *Piece of liver removed at 10:30 a. m. Sections show two fifths to one half necrosis, and slight surrounding cell injury, very little fat.*

Regenerated on carbohydrate diet.

TABLE 4.—THYROID FEEDING

Experiment	Diet	Chloroform	Liver Injury		Remarks
			Central Necrosis	Fat	
23 (Adult 18-124)	3 gm. powdered thyroid daily, 4 days	1½ hr.	2/5-1/2	Trace	Cells somewhat vacuolated beyond actual necrosis
	Starvation 4 days (control)	1½ hr.	1/2	1/3; moderate	Cells somewhat vacuolated beyond actual necrosis
24 (Pup 19-43)	Thyroid and sugar	1 hr.	0	0	Nests of cells suggesting beginning abscesses
25 (Pup 19-47)	Thyroid and cottonseed oil	1 hr.	3/5-2/3	Light; in necrosis	
26 (Pup 19-47)	Thyroid and kidney	1 hr.	0	Trace	

EXPERIMENT 23.—*Fasting Control.*—Dog 18-124 (continued).

Oct. 11: Wt., 13.75 lbs. Isolated for starvation before daily feeding; active.

Oct. 12: Wt., 13.44 lbs.; Oct. 13, Wt., 12.25 lbs.; *fasting*.

Oct. 14: Wt., 13 lbs. In good condition; fourth day of fasting. *Chloroform for one and one fourth hours (from 2 to 3:15 p. m.).*

Oct. 15: Wt., 12.44 lbs. Bright and active; fat diet.

Oct. 16: Wt., 12.38 lbs. Fat diet.

Piece of liver removed at 3:30 p. m. Sections show one half necrosis; fat over one third, moderate; some vacuolated, injured cells surrounding necrosis.

Regeneration on fat diet.

EXPERIMENT 24.—*Thyroid + Sugar Diet.*—Dog 19-43, a black mongrel female pup.

Oct. 22: Wt., 5.25 lbs. Isolated for feeding; mange is very bad, but pup is extremely active; previously on kidney diet; operative wound healed. *Diet consists of 10 gm. glucose, 50 gm. cane sugar, 1 gm. thyroid powder, and kaolin in 100 c.c. water by stomach tube.*

Oct. 23: Wt., 4.9 lbs; Oct. 24, Wt., 4.75 lbs.; *sugar and thyroid as before.*

Oct. 25: Wt., 4.63 lbs. *Cane sugar increased to 60 gm.; other constituents as before.*

Oct. 26: Wt., 4.44 lbs. Very skinny; mange getting worse; diet same as yesterday. *Chloroform for one hour (from 3:30 to 4:30 p. m.).*

Oct. 27: Wt., 4.3 lbs. Somewhat dull; beef extract by stomach tube.

Oct. 28: Found dead.

Necropsy Report.—*Skin* shows extensive mange; fat is atrophied throughout; *liver* is somewhat engorged; no necrosis apparent; perhaps a trace of fat; *left lung* shows atelectasis and hypostasis laterally in lower lobe; other organs negative.

Microscopic Report.—*Lungs:* Atelectasis; edema; a few round cells and multinuclears. *Liver:* no fat; no central necrosis; cell nests of focal necrosis. *Kidneys:* focal necroses.

EXPERIMENT 25.—*Thyroid and Cottonseed Oil Diet*.—Dog 19-47, a black mongrel female pup.

Oct. 22: Wt., 5.2 lbs. Isolated for feeding; quite active; previously on kidney-thyroid diet; wound is healed; 35 c.c. *cottonseed oil*, 1 gm. *thyroid powder*, and 40 c.c. water mixed and given by stomach tube.

Oct. 23: Wt., 4.94 lbs.; Oct. 24, Wt., 4.88 lbs.; oil and thyroid as before.

Oct. 25: Wt., 4.8 lbs. Oil increased to 40 c.c.; 1 gm. thyroid as before.

Oct. 26: Wt., 4.63 lbs. Oil and thyroid as yesterday. *Choloroform* for one hour (from 3:30 to 4:30 p. m.).

Oct. 27: Wt., 4.8 lbs. Active: mixed food; gelatin.

Oct. 28: Wt., 4.7 lbs. Active; gelatin by stomach tube. *Piece of liver removed* at 2:30 p. m. Necrosis three fifths to two thirds; fat +.

Oct. 29: Wt., 4.44 lbs. Dull: mange bad; gelatin diet.

Oct. 30: Found dead.

Necropsy Report.—Mange very bad; emaciated; *thymus* and *mediastinal lymph nodes* quite red; *liver* still shows severe injury—necrosis and fat; other organs negative.

Microscopic Report.—*Liver*: much cell debris removed; one third to two fifths unrepaired; a little fat in lobule centers. *Kidneys*: pyelonephritis.

EXPERIMENT 26.—*Thyroid and Kidney Diet*.—Dog 19-47, a black mongrel female pup.

Oct. 4: Wt., 5.9 lbs. Isolated for feeding; pup is 10 weeks old; has mange and many fleas; very active and noisy; 130 gm. ground *kidney* and 1 gm. *thyroid powder*.

Oct. 5: Wt., 5.75 lbs.; 140 gm. *kidney* and 1 gm. *thyroid*.

Oct. 6: Wt., 5.7 lbs.; 150 gm. *kidney* and 1 gm. *thyroid*.

Oct. 7: Wt., 5.7 lbs.; 150 gm. *kidney* and 1 gm. *thyroid*.

Oct. 8: Wt., 5.63 lbs.; 50 gm. *kidney* and 1 gm. *thyroid*. *Choloroform* for one hour (from 9:30 to 10:30 a. m.).

Oct. 9: Wt., 5.44 lbs.; 150 gm. *kidney* and 1 gm. *thyroid*; clinically all right.

Oct. 10: Wt., 5.38 lbs.; 150 gm. *kidney* and 1 gm. *thyroid*. *Piece of liver removed* at 3 p. m. Sections show *no necrosis*; trace of fat.

Hunt's observations on the protective action of thyroid against acetone poisoning suggested the use of thyroid in some of our experiments. The effect of large doses of thyroid in increasing oxidation and protein break down is well recognized.

Schryver²¹ and, later, Morse²² have studied the autolysis in vitro of livers from thyroid-fed animals. Whipple and Christman²³ have shown that thyroid insufficiency causes no change in the liver function as measured by phenoltetrachlorophthalein. Burge²⁴ has found that thyroid feeding increases the catalase content of blood, and decreases it in the heart, and probably in fat, and skeletal muscles. He has suggested that the increased rate of oxidation may be due to the increased catalase in the blood, while decreased catalase in heart, skeletal muscles and fat may account for increased autolysis in these tissues, for, since oxidation is low, less autolyzing enzymes are destroyed, and autolysis increases.

21. Schryver, S. B.: J. Physiol. 32:159, 1905.

22. Morse, M.: J. Biol. Chem. 22:125, 1915.

23. Whipple, G. H., and Christman, P. W.: J. Exper. M. 20:297, 1914.

24. Burge, W. E., Kennedy, J., and Neill, A. J.: Am. J. Physiol. 43:433, 1917.

Kuriyama²⁵ has reported that in thyroid-fed rats the storage of glycogen does not occur readily, even on very high carbohydrate intake. Also, glycogen disappears rapidly on feeding thyroid under normal conditions. The diastase content of blood and liver remains about normal; the disappearance is probably accounted for by increased metabolism.

The experiments in Table 4 indicate that thyroid feeding has no influence on liver injury following chloroform anesthesia. The thyroid powder employed was a commercial preparation (Armour's). This preparation had been tested in metabolism experiments, and it was shown that the amounts given would increase the fasting level of nitrogen urinary excretion at least 50 per cent. above normal. Experiment 23 shows practically an identical amount of necrosis after thyroid feeding, and after simple starvation. The pups which were given 1 gm. of thyroid daily in addition to their regular food showed the amount of necrosis which we expect following the same diets without thyroid. The only unusual point about the series is that very little fat was found in the injured livers. This may have been due to an increased oxidation; or it may be coincidence in this particular series. An animal fed 3 gm. thyroid daily for four days, followed by hydrazin sulphate subcutaneously, showed the typical fatty liver of hydrazin poisoning. It may be worth mentioning that two rats fed fat plus thyroid, then chloroformed, died a day sooner than the controls receiving fat alone.

TABLE 5.—DIETS OF SKIM MILK; CASEIN AND GELATIN

Experiment	Diet	Chloroform	Liver Injury		Remarks
			Central Necrosis	Fat	
27 (Pup 3a)	Skim milk	1 hr.	0	1/2; slight, diffuse	Glycogen +
28 (Pup 19-45)	Casein and cracker meal	1 hr.	0	Trace	
29 (Pup 19-45)	Casein	1 hr.	0	0	
30 (Adult 19-91)	Casein	1 1/4 hr.	0	0	Slight congestion
31 (Pup 4a)	Gelatin	1 hr.	2/5	Narrow zone around necrosis	Fibrin low
32 (Pup 5a)	Gelatin and sugar	1 hr.	Trace	1/2; moderate	Glycogen +
33 (Pup 19-45)	Alfalfa meal and cracker meal	1 hr.	1/2-3/5	Heavy to periphery	Did not seem to eat very much, but maintained weight very well

EXPERIMENT 27.—*Skim Milk Diet*.—Pup 3a, a black female mongrel.

May 14: Isolated; starvation; apparently in good health; active and lean.

May 15: Wt., 5.05 lbs. Feeding begun; *skim milk ad lib.*

May 16: Wt., 5.06 lbs.; May 17, Wt., 5.4 lbs.; *milk* as before.

May 18: Wt., 5.25 lbs. *Milk* early in morning. *Choloroform* for one hour (from 10:30 to 11:30 a. m.).

May 19: Wt., 4.56 lbs. Seemed to lose appetite temporarily, but continues lively; *milk* continued.

May 20: Wt., 5.0 lbs. Sacrifice in a. m.; blood urea 32 mg.; urea N., 15 mg.; fibrin, 310 mg. per 100 c.c. plasma.

Necropsy Report.—*Liver*: weight, 88 gm.; central veins are, perhaps, slightly more prominent than normal; *kidneys* contain many small cysts, 2 mm. in diameter.

Microscopic Report.—*Liver*: no necrosis; very slight amount of diffuse fat; considerable glycogen present, especially in peripheral zones; central areas stain darker. *Kidneys* are cystic, probably congenital.

EXPERIMENT 30.—*Cascin Diet.*—Dog 19-91, a large male hound.

Dec. 23: Wt., 49.0 lbs. Isolated, after daily feeding; dog is healthy and active.

Dec. 24: Wt., 48.5 lbs. Feeding begun; 100 gm. *cascin* made into mush and given by spoon.

Dec. 25-27: 100 gm. *cascin* daily.

Dec. 28: Wt., 44.75 lbs. Active and bright. *Chloroform* one and one fourth hours (from 9 to 10:15 a. m.).

Dec. 29: Wt., 43.4 lbs. Not as active as usual; gelatin diet.

Dec. 30: Wt., 42.2 lbs. Quiet; gelatin diet. *Piece of liver* removed at 3 p. m. Sections show no necrosis and no fat; tissue looks normal; slight congestion.

Dec. 31: Wt., 42.06 lbs. Experiment discontinued.

EXPERIMENT 31.—*Gelatin Diet.*—Pup 4 a, a black and white female mongrel.

May 23: Isolated; starvation; pup is probably about 4 months old; still has puppy teeth, but fur is replaced by coarse hair of adult.

May 24: Wt., 6.44 lbs. Feeding begun; 25 gm. *gelatin* + salt and kaolin, dissolved and divided into two daily feedings by stomach tube.

May 25: Wt., 6.3 lbs.; May 26, Wt., 6.3 lbs.; *gelatin* as before; very lively.

May 27: Wt., 6.0 lbs. *Choloroform* for one hour (from 10:50 to 11:50 a. m.).

May 28: Wt., 5.88 lbs. Continues very active.

May 29: Wt., 5.75 lbs. Sacrificed in a. m.; blood urea, 29 mg.; urea N., 13.4 mg.; fibrin, 80 mg. per 100 c.c. plasma.

Necropsy Report.—Clots flabby. *Liver*: weight, 91 gm. Lobule centers large and red, representing probably one third or more necrosis, surrounded by an opaque area of fat; peripheries translucent and normal; remaining viscera normal in gross.

Microscopic Report.—*Liver*: about two fifths central necrosis, with congestion and some collapse; a little fat at edge of necrosis, extending into the latter, and out in the less affected tissue. Spleen is hyperemic; giant cells numerous.

EXPERIMENT 32.—*Gelatin and Carbohydrate Diet.*—Pup 5 a, a collie, male.

June 3: Isolated; starvation; pup is about 2 months old; bright and active.

June 5: Wt., 6.25 lbs. Feeding begun; mixture given by stomach tube consisted of 25 gm. *gelatin* and 25 gm. cane sugar daily; rice and potatoes left in cage, but not touched.

June 6: Wt., 6.06 lbs. *Gelatin* and *sugar* as before.

June 7: Wt., 6 lbs. *Sugar* increased to 35 gm.; *gelatin* still 25 gm.

June 8: Wt., 6 lbs. *Chloroform* for one hour (from 10:25 to 11:25 a. m.); food as yesterday.

June 9: Wt., 5.94 lbs. Lively; mixture by stomach tube as before.

June 10: Wt., 5.94 lbs. Sacrificed in a. m.; blood urea, 48 mg.; urea N., 23 mg.; fibrin, 135 mg. in 100 c.c. plasma.

Necropsy Report.—*Liver:* weight, 156 gm.; necrosis not apparent in gross; central one half to three fifths of lobules look yellow and opaque; no gross lesions in other organs.

Microscopic Report.—*Liver:* Occasional necrotic cells; moderate amount of fat in central half of lobules; large deposits of glycogen in peripheral two thirds.

EXPERIMENT 33.—*Alfalfa Meal Plus Cracker Meal Diet.*—Dog 19-45, a black mongrel female pup.

Oct. 4: Wt., 9.13 lbs. Isolated for feeding; pup is 10 weeks old; has mange; very active and noisy; 100 gm. *alfalfa meal* + 50 gm. *cracker meal*; mixture cooked; ate one third.

Oct. 5: Wt., 8.94 lbs. Mixture *alfalfa meal* and *cracker meal* half and half.

Oct. 6: Wt., 8.94 lbs. Mixture as yesterday, moistened with juice of boiled liver.

Oct. 7: Wt., 8.94 lbs.; 100 gm. *alfalfa meal* + 100 gm. *cracker meal* boiled; eats a little.

Oct. 8: Wt., 8.7 lbs. Mixture *ad lib.*; does not eat very much. *Chloroform* for one hour (from 9:30 to 10:30 a. m.).

Oct. 9: Wt., 8.38 lbs. Liver diet; active; does not appear sick.

Oct. 10: Wt., 8.5 lbs.; liver diet. *Piece of liver removed* at 1:45. Sections show one half to three fifths necrosis and heavy deposits of fat to periphery. Regeneration on liver diet.

Skim milk seems to be a diet quite protective against chloroform injury. Considering the results obtained from casein feeding, also presented in Table 5, it is obvious that skim milk contains two protective substances: sugar and casein; the only difficulty in attaining protection is the necessary consumption of large quantities of fluid, and this is possible with pups, at least. The protection afforded dogs by a casein diet seems to be very complete, since even the large, active adult dog, 19-91, showed no subsequent injury. A small series of rats showed a slight, irregular protection to chloroform injury following a diet of cottage cheese.

The one experiment in feeding gelatin alone suggests an inefficient protection; Experiment 32 indicates that the lack of protection from gelatin (unlike that of fat) does not detract from the protective action of sugar feeding. Whether the difference here noted between casein and gelatin is associated with their relative ability to yield sugar in the body metabolism, or with some other factor, it is difficult to say.

No doubt Experiment 33 may be interpreted to mean that, although the pup ate enough of the bulky mush to maintain weight, enough of the carbohydrate, cracker meal, was not ingested to afford protection; and that the alfalfa meal was not of equal value in the rôle of protective food. From the amount of injury, it may be argued that the mixture was actually harmful, but it seems more likely that the alfalfa meal acted simply as roughage and not as food in the dog's digestive economy.

TABLE 6.—SUGAR AND FAT INTRAVENOUSLY DURING ANESTHESIA; AMINO-ACIDS SHORTLY BEFORE ANESTHESIA

Experiment	Diet	Chloroform	Liver Injury		Remarks
			Central Necrosis	Fat	
34 (Adult 19-28)	Starvation 4 days (control)	1¼ hr.	3/5	Moderate throughout	
	Starvation 4 days. 15-20 gm. casein digest 15 min. before chloroform	1¼ hr.	2/5	Moderate throughout	
35 (Adult 18-135)	Starvation 3 days. 200 c.c. cream intravenously during chloroform	1½ hr.	3/5	Heavy to periphery	Septicemia; died from combination of injuries
36 (Adult 18-56)	Starvation 3 days. 460 c.c. 10% glucose intravenously during chloroform	1½ hr.	4/5	Moderate throughout	Fatal injury

EXPERIMENT 34.—*Starvation (Control).*—Dog 19-28, a fox terrier, male adult.

Nov. 29: Wt., 19 lbs. Isolated for starvation; quiet; very fat.

Nov. 30: Wt., 18.2 lbs.

Dec. 1: In good condition.

Dec. 2: Wt., 17.63 lbs.; still fat. *Chloroform for one and a quarter hours* (from 9:45 to 11 a. m.).

Dec. 3: Wt., 17.25 lbs. Gave gelatin; vomited; not sick in appearance.

Dec. 4: Wt., 16.7 lbs. Gave gelatin; vomited. *Piece of liver removed* at 4 p. m. About three fifths necrosis; fat ++.

Dec. 5: Wt., 16.13 lbs. Wound bleeds somewhat; vomits gelatin; feeding experiment discontinued.

EXPERIMENT 34.—*Starvation; Amino-Acids Just Before Chloroform.*—Dog 19-29 (continued); fox terrier, male adult.

Dec. 18: Wt., 17.25 lbs. Isolated for starvation; bright and in good condition, except that abdominal wound has a slight superficial sinus.

Dec. 19 to 20: No food.

Dec. 21: Wt., 15.8 lbs. Bright and healthy. *Chloroform for one and a quarter hours* (from 11:15 to 12:30). Gave between 15 and 20 gm. *casein digest* by stomach tube a few minutes before anesthesia; digest contains 63.7 mg. amino-nitrogen per gram. Lean meat *ad lib.* in p. m.

Dec. 22: Wt., 16.2 lbs. Meat diet; eats well; not sick clinically.

Dec. 23: Wt., 16 lbs. Meat *ad lib.* Piece of liver removed at 2:30 p. m. Sections show two fifths necrosis; fat ++. Regenerated on lean meat.

EXPERIMENT 35.—*Cream Intravenously at Time of Anesthesia.*—Dog 18-135, a long-haired, black male (old dog).

June 15: Wt., 55.6 lbs. Isolated (after daily feeding); starvation; water *ad lib.*; dog is bright and active.

June 16 to 17: Fasting.

June 18: Wt., 51.5 lbs. *Chloroform for one and a half hours* (from 2:50 to 4:20 p. m.). Gave intravenously during anesthesia 200 c.c. of *cream* from the top of a quart of milk, mixed with 200 c.c. of physiologic sodium chlorid solution.

June 19: Wt., 52.4 lbs. Quite sick; very thirsty; gave the dog liver to eat.

June 20: Wt., 51.1 lbs. Better clinically; ate liver well. *Piecc of liver* removed at 1:30 p. m.

June 21: Found dead.

Necropsy Report.—Evidence of septicemia (from nonpasteurized cream). *Hcart:* Blood partially clotted (body still warm). Subepicardial and subendocardial hemorrhages; two subendocardial infarcts in left ventricle; small myocardial abscesses; old thickening and apparent shrinkage of mitral flaps. *Lungs:* Right lung shows a thrombus in middle lobe; left is atelectatic in lateral border of lower lobe.

Liver: weight, 799 gm.; very friable; red dots of central necrosis, and fat deposits to lobule periphery; frequent opaque, white spots of various sizes suggest abscesses. *Splcen:* fibrous; no pulp reaction noticeable. Kidneys: capsule strips with slight resistance leaving a rough surface; abscesses visible on surface; cortices swollen, markings blurred, opaque patches and streaks (evidently acute nephritis).

Microscopic Report.—*Hcart:* endocarditis and myocarditis. *Lungs:* hemorrhages and some consolidation; fat in vessel walls, thrombi, and in inter-alveolar tissue. *Liver:* about three fifths necrosis; practically all of remainder is fatty; much brown pigment. *Pancrcas* congested. *Kidneys:* severe nephritis, especially of tubules; interstitial edema; abscess formation; casts, etc.; diffuse fat in epithelium of collecting tubules, and in blood vessels (apparently thrombosed).

EXPERIMENT 36.—*Glucose Intravenously at Time of Anesthesia.*—Dog 18-56, a brindle and white bull, female.

June 10: Wt., 20.8 lbs. Isolated; starvation; in good condition; extremely active; Water *ad lib*.

June 13: Wt., 18.4 lbs. Chloroform for one and a half hours (from 3:10 to 4:40 p. m.); 10 per cent. solution of glucose given continuously during anesthesia; 460 c.c. in all.

June 14: Wt., 17.63 lbs. Quieter than usual; thirsty.

June 15: Wt., 18.06 lbs. Appears dull. *Piece of liver* removed at 9:30 a. m.

June 16: Found dead.

Necropsy Report.—Slight amount of free blood in peritoneal cavity, evidently due to deficiency in clotting at point of operation in liver. Blood in heart is partially clotted; clots flabby, like soft jelly. Spots on posterior surface of lungs look suspicious of hemorrhage. *Liver:* weight 267 gm.; appears to have about one half necrosis, surrounded by a zone of fat, and a narrow rim of normal tissue. *Splcen* has knobby projections, evidently of hemorrhage; other viscera negative.

Microscopic Report.—*Liver:* necrosis of four fifths; fatty throughout. There seems to have been a slight removal of necrotic cell debris between operation and death.

Glucose or cream intravenously during anesthesia seems to have little effect on the liver injury resulting from chloroform. It is even possible that the glucose solution (Experiment 36) may have had a deleterious effect, since the necrosis is so extreme. It will be noted that the necrosis in the case in which cream was injected is less intense than in the case in which sugar was introduced. Positions are reversed when these substances are fed in the days previous to chloroform

anesthesia. No doubt it will be suggested by some one that the fat in the blood stream "fixed" a large percentage of the chloroform which might otherwise have injured the liver. Such may have been the case, but the liver sustained a severe injury, notwithstanding. The dog receiving cream (Experiment 35) showed septicemia, but this did not modify the liver picture appreciably, since the central necrosis occurred before the septicemia developed.

We lost two valuable dogs in the attempt to give a solution of amino-acids intravenously during the administration of chloroform anesthesia. A previous injection of some of the same material into a normal, unanesthetized animal had produced no reaction, but the combination with chloroform was fatal. To surmount this difficulty, a third dog was given casein digest in weak acid a few minutes before the anesthetic was started, with the idea that the amino-acids would be passing into the portal circulation during the period of chloroform anesthesia. The result shows a small but quite definite lessening of necrosis as compared with a simple starvation control on the same animal. We should remember that these amino-acids resulted from the digestion of casein which by itself has such a marked protective action against chloroform poisoning.

Burge²⁶ has shown that catalase, supposed by him to govern oxidations, is decreased very extensively in chloroform anesthesia. On the other hand, the ingestion of foodstuffs increases this enzyme. Proteins have the greatest power in this respect, the amino-acids being the stimulating principles; fats are less powerful stimulants than proteins, but more efficient than carbohydrates; the glycerin radical acts in the case of fats, and the simple sugars, principally dextrose, in the case of carbohydrates. Casein has been shown to be very efficient in causing an increase in catalase. It is understood that the increase in catalase from the ingestion of foodstuffs is more or less temporary, being most noticeable during the period of digestion. Burge has found a decrease in catalase during starvation, but has reported very little regarding the catalase level maintained by individual diets through the course of feeding experiments lasting several days.

It would seem, therefore, that a substance tending to increase the enzyme catalase in a given period would tend to neutralize the action of a concurrent chloroform anesthesia, providing, of course, that

26. Burge, W. E.: *Science* **46**:618, 1917; *J. Pharm. and Exper. Therap.* **12**: (Nov.) 1918; *Am. J. Physiol.* **47**:351, 1918. Burge, W. E., and Neill, A. J.: *Am. J. Physiol.* **43**:58, 1917; *idem.* **45**:500, 1918; *idem.* **46**:117, 1918; *idem.* **47**:13, 1918. Burge, W. E., Neill, A. J., and Ashman, R.: *Am. J. Physiol.* **45**:388, 1918.

chloroform produces its effect either as an anesthetic or as a protoplasmic poison, or both, by a reduction of oxidation. Such a neutralizing effect was not produced by injecting either sugar or fat; the result with casein digest is more suggestive, but far from conclusive.

GENERAL DISCUSSION

No adequate explanation is offered for the protective or injurious effect of any diet in modifying the action of chloroform. It will be recalled that Graham correlated resistance with glycogen content of the liver. This is an attractive theory, and seems to hold true in some cases. Carbohydrate diets certainly build up liver glycogen; the storage can be readily seen in ordinary hemotoxylin and eosin stained sections. However, if Kuriyama's work is reliable, glycogen storage is very difficult, and glycogen elimination is very prompt when thyroid is given; yet in our series of experiments the protective action of sugar or kidney is not changed by the addition of thyroid, and thyroid alone previous to chloroform does not modify the picture of ordinary starvation plus chloroform.

Furthermore, it is difficult to see why brain, which has practically no free carbohydrate, should be protective; and why kidney and liver should be so much more protective than skeletal muscle. It is true that liver, especially, has an appreciable carbohydrate content, but it is scarcely credible that such a small difference in percentage between liver and muscle should make a recognizable difference in liver susceptibility. The beef extract which we used contained only a trace of reducing substances (Fehling's test) and showed no more after acid hydrolysis; yet this extract in relatively small amounts built up a distinct resistance to the action of chloroform, or at least prevented the development of a susceptibility. The casein used in our feeding experiments was free from reducing sugars (Fehling's test) both before and after acid hydrolysis, yet this casein was a highly protective food. We do not mean to intimate that these proteins, and simpler nitrogenous products are not capable of yielding sugars in the process of body metabolism, and that the sugars so formed might not be stored as glycogen under certain conditions, but the evidence is not clear in every case. The preferability of certain proteins, for example, casein, or kidney proteins, over other proteins, for example, gelatin or skeletal muscle, for sugar formation is more or less conjectural. It may be that the ingested food does not form liver glycogen itself, but has a sparing action on the glycogen already stored, insofar as it is able to furnish the fuel for heat and energy. This is conjecture again;

we usually speak of carbohydrates sparing proteins, rather than the reverse. Moreover, fat, which is an excellent fuel, has no such action.

Opie's idea that ingested fat is stored, partly by the parenchymatous organs, and that the "fixing" of chloroform by this fat results in a greater injury to the cells in certain localities, will hardly explain the severe injury sustained by starved animals.

Whatever the protective action may be, it certainly seems to be built up by the body, and does not lie in the foods as such. This is indicated by the lack of protection given by glucose when injected intravenously during chloroform anesthesia.

SUMMARY

Starved animals are very susceptible to liver injury from chloroform. A maximal injury is to be expected.

Sugar, and diets rich in carbohydrates, fed in the days preceding chloroform anesthesia, exert a marked protective action against liver injury.

Fat alone, or combinations of food containing fat in large proportion, induce a maximal susceptibility to liver injury comparable to starvation.

Skeletal muscle and heart muscle seem to have a slight protective action.

Beef extract is highly protective in proportion to its actual food value.

The parenchymatous organs, liver and kidney exert a considerable amount of protection.

Brain, although rich in lipoidal substances, is a protective food against chloroform injury, thus being in marked contrast to fat mixtures.

Skim milk alone, and commercial casein alone, or in combination with cracker meal, are highly protective diets.

Gelatin has but slight protective action itself, but when given in mixtures with sugar, does not lessen the protective value of the latter.

Thyroid powder, given alone, or in combination with foods (sugar, fat, etc.) apparently does not modify the chloroform injury which is to be expected without such addition.

Glucose, or cream, given intravenously during chloroform anesthesia, do not modify the effect of the drug on a starved animal. One instance in which casein digest (high in amino-acid content) was given by stomach tube a few minutes before chloroform anesthesia, indicates a slight protective action.

No single theory so far advanced will explain this peculiar protective action of certain food substances against the liver injury of chloroform anesthesia. It certainly is a reaction of the liver cells, not of substances circulating in the blood stream.

These facts should not be lost sight of in the management of any human cases in which chloroform is indicated. The patient should be given liberal amounts of carbohydrates and milk for at least two days preceding the anesthesia. It can not be too often emphasized that it is dangerous to give chloroform to man or animal whenever a fasting period has preceded the administration of the anesthetic.

THE INFLUENCE OF DRUGS AND CHEMICAL AGENTS ON THE LIVER NECROSIS OF CHLORO- FORM ANESTHESIA *

PAPER II

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SAN FRANCISCO

Among the various explanations offered for the well known chloroform livery injury, the theory of Graham¹ is, perhaps, the most attractive. This author believes that in the presence of water and oxygen in the body, chloroform is split and hydrochloric acid and carbon dioxid are formed; the hydrochloric acid then kills a certain amount of liver parenchyma, either by direct action or by secondary asphyxia. We must admit that we are unable to follow the chemical reactions as outlined by Graham. Furthermore, it is just as difficult to explain chloroform necrosis as to explain why chloroform passes by all body tissues until it reaches the liver, where the hypothetical chemical reaction takes place with release of hydrochloric acid. The specific susceptibility of the liver cell for chloroform is the riddle which has so far defied solution. Graham produced liver necrosis in dogs by injecting hydrochloric acid into the portal vein; the necrosis differed from typical chloroform injury in being portal (peripheral) rather than central. Hydrochloric acid given by stomach tube to rabbits generally proved fatal; at necropsy the animals were found to have fatty livers, and hemorrhages in the stomach and duodenum. He found that the areas of central necrosis in chloroform poisoning gave an acid test with neutral red, and a chlorin test with silver nitrate and sunlight.

Graham records experiments in which sodium carbonate in hypertonic saline solution, given intravenously during chloroform anesthesia markedly inhibited the production of necrosis, although the fatty changes were comparable to the controls which received normal saline only. Furthermore, it was found that central liver necrosis followed the use of: (1) dichlor- and tetrachlor-methane (in proportion to the chlorin content); (2) tribrom- and tri-iodo-methane; (3) monochlor-, monobrom-, monoidodo-, and dibrom-ethane (in pro-

* From the George Williams Hooper Foundation for Medical Research, University of California Medical School.

1. Graham, E. A.: *J. Exper. M.* **22**:48, 1915; *J. Biol. Chem., Proc.* **20**:25, 1915; *J. A. M. A.* **69**:1666, 1917; *Am. J. Surg., Quart. Sup. Anesth.* 1917, p. 34; *Dental Summary* **37**:506, 1917; *J. Nat. Dent. Assn.* **4**:733, 1917.

portion to the ease of formation of halogen acids). In some cases an increase of the neutral salts of the halogen acids could be demonstrated subsequently in the urine. Ether and chloral hydrate, which do not yield halogen acids, do not form necroses, but give only edema, and fat infiltration to a less degree.

We have attempted to repeat Graham's observations on the protective action of sodium carbonate given intravenously during chloroform anesthesia. He administered the anesthetic over a period of four and one-half hours. We have found that liver injury is much more uniform after a preliminary starvation; this renders the animals more susceptible to injury, hence a shorter period of anesthesia is advisable. Our usual procedure is to give one and one-half hours of chloroform anesthesia (drop method, with personal attention) to dogs which have fasted three days, and one and one-quarter hours to those which have fasted four days. Graham gave his solutions through a cannula in the saphenous vein; we have given the fluid into the external jugular vein, through a needle attached by tubing to a raised funnel. Graham used a hypertonic saline solution of sodium carbonate, 10 gm. Na_2CO_3 and 14 gm. NaCl per liter of water; we have made up similar solutions in each case. A perusal of Graham's protocols shows that to one dog he gave $33\frac{1}{2}$ c.c. of carbonate solution per kilogram, and to the other 30 c.c. per kilogram; in our series we gave 34 c.c. per kilogram to the first dog, 30 c.c. per kilogram to the second, 33.8 c.c. per kilogram to the third, and $35\frac{1}{4}$ c.c. per kilogram to the fourth. Instead of sacrificing on the second day, we have removed a small piece of liver under ether anesthesia on the second day; the technic of this procedure is discussed more fully in the preceding article of this series. Tissue has been fixed with formaldehyd solution, and both hematoxylin and eosin, and fat stains made.

The following table and protocols indicate the results of our experiments. These experiments indicate that Graham's claims are based on incomplete or inaccurate observations. Carefully controlled experiments show beyond a reasonable doubt that carbonates given intravenously or by mouth have no effect whatsoever on the injurious action of chloroform on the liver. Graham gives no statements concerning the diets in his experiments and we are inclined to believe that the diet conditions must explain his observations.

EXPERIMENTAL OBSERVATIONS

It will be observed in all the tables that the amount of liver necrosis is estimated in fractions, $\frac{1}{2}$, $\frac{2}{3}$, etc. This means that inspection of the microscopic sections gave clear histological evidence of a uniform typical hyaline necrosis involving each lobule to the extent of $\frac{1}{2}$ or $\frac{2}{3}$

of all the cells of these lobules. The necrosis is invariably central and unless otherwise stated is clear cut and uniform throughout. All the evidence shows that there is great uniformity in this reaction—one group of liver lobules, therefore, gives a true picture representing all the liver lobules or the whole organ.

TABLE 7.—INTRAVENOUS INJECTION OF BUFFER SOLUTIONS DURING CHLOROFORM ANESTHESIA

Experiment	Starvation, Days	Supplementary Treatment During Anesthesia	Chloroform, Hours	Liver Injury		Remarks
				Central Necrosis	Fat	
40 (Dog 18-82)	3	Sodium carbonate in hypertonic saline intravenously	1½	1/2 to 3/5	1/2; moderate	Previously on metabolism; sugar feeding
41 (Dog 19-5)	3	Sodium carbonate in hypertonic saline intravenously	1½	1/4 to 1/3	Scattered to periphery	Cytoplasmic injury severe up to 1/2
42 (Dog 19-6)	3	Normal saline intravenously (control)	1½	1/4 to 1/3	Trace	Cytoplasmic injury severe up to 1/2
43 (Dog 19-6)	3	Sodium carbonate in hypertonic saline intravenously	1½	1/4 to 1/3	Moderate to periphery	Cytoplasmic injury severe up to 1/2
44 (Dog 19-74)	4	Sodium carbonate in hypertonic saline intravenously	1¼	1/2 +	Trace; diffuse throughout	
	4	No injection (control)	1¼	1/2	1/3; moderate	
45 (Dog 18-131)	3	Phosphate solution intravenously	1½	3/4	1/4; heavy	Moribund at time of sacrifice on second day
46 (Dog 19-9)	3	Phosphate solution intravenously	1½	3/4 to 4/5	Light to periphery	Death shortly after operation on second day

EXPERIMENT 40.—*Carbonate Intravenously During Chloroform Anesthesia.*—Dog 18-82, a young, white, female bull.

June 8: Wt., 20.3 lbs. Isolated after daily feeding; previously on metabolism, with sugar feeding; active; somewhat skinny; one of old incisions has a superficial discharging pocket.

June 9 to 10: No food.

June 11: Wt., 18.63 lbs. *Chloroform* for one and a half hours (from 1:50 to 3:20). During the first hour of anesthesia 290 c.c. of the following solution was given intravenously: 5 gm. Na_2CO_3 , and 7 gm. NaCl in 500 c.c. water. Took anesthesia poorly; recovered from effects slowly.

June 12: Wt., 18.63 lbs. Very lively.

June 13: Wt., 17.56 lbs. *Piece of liver removed* at 2 o'clock. Lost considerable blood. Gave epinephrin subcutaneously. Sections show one half to three fifths necrosis, with almost all the remaining tissue fatty. Regenerated on bread and milk.

EXPERIMENT 41.—*Carbonate Intravenously During Chloroform Anesthesia.*—Dog 19-5, an adult male airdale.

July 15: Isolated before daily feeding; starvation.

July 16: No food.

July 17: Wt., 26.75 lbs. *Chloroform for one and a half hours* (from 3:50 to 5:20). Gave intravenously during first fifty minutes of anesthesia: 3.6 gm. Na_2CO_3 and 5.4 gm. NaCl in 360 c.c. water.

July 18: Wt., 26.25 lbs. Apparently as well as usual: fat diet.

July 19: Wt., 26.13 lbs. Vomited about 2 o'clock; fat diet. *Piece of liver removed at 2:45 p. m.* Sections show a necrosis of one fourth to one third, with intense cytoplasmic injury up to one half (swollen cells without visible cytoplasm), and a scattering of fat throughout. Regenerated on fat diet.

EXPERIMENT 42.—*Saline Intravenously During Chloroform Anesthesia.*—Dog 19-6, a yellow adult male mongrel.

July 17: Wt., 30.5 lbs. Isolated after daily feeding; healthy and active.

July 18 to 19: Fasting.

July 20: Wt., 28.25 lbs. *Chloroform for one and a half hours* (from 9:15 to 10:45 a. m.); 400 c.c. M/6 NaCl intravenously during first hour of anesthesia.

July 21: Wt., 26.96 lbs. Very active. Lean meat diet.

July 22: Wt., 27.13 lbs. *Piece of liver removed at 11 o'clock.* Sections show very little fat; actual necrosis of one fourth to one third, with severe cytoplasmic reaction up to one half (cells swollen with very little cytoplasm). Regenerated on lean meat diet.

EXPERIMENT 43.—*Carbonate Intravenously During Chloroform Anesthesia.*—Dog 19-6, a yellow adult male mongrel.

Aug. 16: Wt., 30.2 lbs. Isolated after daily feeding; operative wounds healed; healthy and active.

Aug. 17 to 18: Fasting.

Aug. 19: Wt., 26.75 lbs. *Chloroform for one and a half hours* (from 9:10 to 10:40 a. m.). Gave intravenously during first hour and ten minutes of anesthesia: 4.1 gm. Na_2CO_3 and 5.74 gm. NaCl in 410 c.c. water.

Aug. 20: Wt., 25.9 lbs. Quieter than usual; fat diet.

Aug. 21: Wt., 25.2 lbs. Eats fat well; bright and active. *Piece of liver removed at 1:15 p. m.* Sections show a practically identical picture to that obtained in previous experiment with saline injection at time of chloroform. Necrosis of one fourth to one third, with severe cytoplasmic reaction up to one half (large, clear cells), fat rather heavy in central areas, and slight to periphery. (More fat than in control.) Regenerated on fat diet.

EXPERIMENT 44.—*Carbonate Intravenously During Chloroform Anesthesia.*—Dog 19-74, a young, black and white male terrier.

Nov. 18: Wt., 13.56 lbs. Isolated for starvation before daily feeding; recovering from distemper; rather mean-spirited; active.

Nov. 19 to 20: Starvation.

Nov. 21: Wt., 12.13 lbs. *Chloroform for one and a fourth hours* (from 8:30 to 9:45 a. m.). Gave intravenously during first forty minutes of anesthesia 1.95 gm. Na_2CO_3 and 2.8 gm. NaCl in 195 c.c. water.

Nov. 22: Wt., 11.9 lbs. Very quiet; thirsty; casein diet.

Nov. 23: Wt., 12.06 lbs. Eats nothing; vomited gelatin given by stomach tube. *Piece of liver removed at 10:30 a. m.* Sections show a strong one half necrosis; fat: trace diffuse throughout. Mixed food.

Simple Starvation and Chloroform (Control).—Dog. 19-74.

Dec. 4: Wt., 12.94 lbs. Isolated for starvation before daily feeding; wound from previous operation has an open spot at lower end of incision; quite active; distemper gone.

Dec. 5 to 6: Starvation.

Dec. 7: Wt., 11.8 lbs. Quite active. *Chloroform for one and a quarter hours* (from 8:30 to 9:45 a. m.): attempted to give NaCl intravenously, but could not get in veins.

Dec. 8: Appears as well as usual.

Dec. 9: Wt., 11.06 lbs. Quite active. *Picce of liver removed at 2 o'clock; bled freely; stopped hemorrhage with a second ligature. Sections show one half necrosis; fat one third, moderate. Regenerated on beef extract.*

EXPERIMENT 45.—*Phosphates Intravenously During Chloroform Anesthesia.*
—Dog 18-131, a brown and white male terrier mongrel.

June 7: Wt., 25.2 lbs. Isolated after daily feeding.

June 8 to 9: No food.

June 10: Wt., 22.63 lbs. *Chloroform for one and a half hours (from 2:50 to 4:20 p. m.); 4 gm. Na_2HPO_4 and 0.1 gm. NaH_2PO_4 in 100 c.c. normal saline were given intravenously during the first half hour of anesthesia. Muscular twitchings were observed during the first hour of anesthesia.*

June 11: Dog active; apparently all right.

June 12: Wt., 19.63 lbs. Found comatose at 9 a. m.; sacrificed; blood urea, 46 mg.; urea N., 21.5 mg.

Necropsy Report.—Blood clots are flabby. *Liver* weight, 272 gm. Lobules show extensive central necrosis, with remaining tissue fatty. *Kidney* cortices look opaque; glomeruli very distinct; no hemorrhages into intestinal tract or elsewhere; two large, red, mediastinal lymph nodes were noticed.

Microscopic Report. *Liver:* about three fourths necrosis; remainder of tissue fatty. *Kidneys:* cloudy swelling.

EXPERIMENT 46.—*Phosphates Intravenously During Chloroform Anesthesia.*
—Dog 19-9, a male collie mongrel.

Aug. 3: Wt., 32.96 lbs. Isolated before daily feeding; starvation.

Aug. 4: No food.

Aug. 5: Wt., 32.13 lbs. *Chloroform for one and a half hours (from 1:45 to 3:15 p. m.). During one hour and ten minutes of anesthesia, gave the following intravenously: 5 gm. Na_2HPO_4 , 0.5 gm. NaH_2PO_4 and 3.5 gm. NaCl in 250 c.c. water. Took the anesthetic all right but vomited a little bile stained fluid afterward.*

Aug. 6: Wt., 30.9 lbs. Weak and dull; vomited sugar; retained potatoes; blood urea, 44 mg.; urea N, 21 gm.

Aug. 7: Wt., 31.25 lbs. Brighter. *Removed picce of liver at 11 a. m; considerable hemorrhage; vomited later; died between 4 and 5 p. m.; necropsy at 5:20 p. m.*

Necropsy Report.—No evidence of clotting, and blood refuses to clot on contact with tissues; peritoneal cavity full of fluid blood seeped from liver operation. *Liver:* weight, 324 gm. Central three fourths of each lobule is gorged with blood, and peripheries are opaque with fat; seepage is from needle holes in liver. *Stomach* and *intestines* contain much blood; mucosa of pyloric antrum is greatly injected—probably the site of hemorrhage.

Microscopic Report.—*Liver:* three fourths to four fifths necrotic; fat in dead tissue, and a little in surrounding cells. *Spleen:* engorged. *Stomach:* pseudo-membrane. *Kidneys:* cloudy swelling and engorgement.

Experiment 40 shows an average amount of injury from one and one-half hours of chloroform. This dog had previously been used for an experiment, the conditions of which were slightly different. On the other occasion there had been seven days of fasting, but 100 gm. of sugar were given a few hours before chloroform anesthesia of one and one-half hours. The injury was not established, but on the fifth day after anesthesia, with sugar feeding each day, the liver was still

$\frac{1}{4}$ unrepaired, with a trace of fat. We may safely conclude that no protective action is exhibited by the carbonate solution in Experiment 40.

Experiment 41 shows a relatively slight injury, but so does Control Experiment 42. These dogs were both good, healthy animals of medium weight, and received exactly the same treatment throughout, except in the solution which they received intravenously. Dog 19-6 was later used for Experiment 43, in which he received carbonate solution. The hematoxylin and eosin stained sections from the three experiments, 41, 42 and 43, might easily be passed as tissue from the same case; the control, 42, shows less fat than either of the other two.

Experiment 44 is really two experiments on the same dog. If there is any difference at all in the two injuries, there is a trace more necrosis after carbonate intravenously during anesthesia than there is when no injection was given. It may be noted that the control experiment with Dog 19-74 was performed after the carbonate experiment, while the reverse is true with Dog 19-6. This only goes to show that two successive injuries in a dog are practically the same, providing that other conditions are similar; for example, starvation period, and length of anesthesia; and that sufficient time is given between experiments to allow complete regeneration and recovery of weight, etc., to take place; the carbonate solution apparently has no influence in the matter.

In view of the supposed protective action of carbonate solution, we decided to try the action of phosphate solutions, since they, also, presumably, would have a buffer effect. Experiments 45 and 46 show the result of such trials. A little monosodium phosphate was added to the disodium phosphate in each case to reduce slightly the alkalinity of the solution, and a total amount was chosen which would certainly have some value as a buffer (from 4 to 6 gm.). From the extreme injury obtained it certainly appears that there was no protection, possibly an added insult. Greenwald² has recently shown that phosphate ion is not toxic, at least in its immediate action. If reference is made to paper III of this series, relative to liver regeneration on starvation and sugar feeding, it will be seen that sodium bicarbonate given by stomach tube either before or after chloroforming has no effect on the nitrogen curve or on the liver injury.

Granting that glycogen storage in the liver lessens the amount of liver necrosis, as Graham³ has claimed, and if his dogs were not starved, another explanation may be offered for the protection observed in his experiments. Pavy and Bywaters⁴ found that postmortem

2. Greenwald, I.: *J. Pharm. and Exper. Therap.* **11**:281, 1918.

breaking of glycogen in the liver can be stopped by an injection of 2 per cent. sodium carbonate into the living animal; Pavy and Godden⁵ were able to stop chloroform or vagus stimulation glycosuria in the cat by injection of carbonate; McDanell and Underhill⁶ have reported a marked reduction of epinephrin glycosuria with carbonate given intravenously in some animals. Therefore, if the animals not receiving the alkaline solution were continually losing sugar from chloroform glycosuria (quite marked in cats) over a period of four and a half hours, the liver glycogen, if it were efficacious, would perhaps be diminished enough to permit injury in Graham's experiments.

TABLE 8.—USE OF EPINEPHRIN, QUININ, STRYCHNIN AND TOXIC PROTEOSE

Experiment	Starvation, Days	Supplementary Treatment	Chloroform, Hours	Liver Injury		Remarks
				Central Necrosis	Fat	
47 (Dog 19-10)	4	Epinephrin subcutaneously on the 2 days preceding chloroform	1	1/4 to 1/3	1/3; scattered	Young, immature dog; developed abscess from injection; sacrificed. Liver necrosis surrounded by a zone of vacuolated cells; glycogen +
48 (Dog 19-4)	4	Epinephrin injection 2 days preceding chloroform	1 1/4	Trace	2/5; moderate	Central areas show injury (large vacuolated cells) but very little necrosis; abscess developed
49 (Dog 19-73)	4	Epinephrin subcutaneously less than 1 1/2 hrs. before chloroform	1 1/4	1/2	Light; in necrosis	Abscess developed; sacrifice on second day; fat mostly in necrotic areas
50 (Dog 18-124)	4	1 gm. quinin sulph. in weak acid by stomach tube daily for 4 days	1 1/4	Trace	Trace	Severe cytoplasmic injury in central 1/3 or 2/5; previous exper. on same dog gave 1/2 necrosis after simple starvation (see Exper. 23)
51 (Dog 19-11)	4	Starvation only (control)	1	2/3 to 3/4	Moderate throughout	Young, immature dog; control to series 19-10, 19-11, 19-12, 19-13, distemper developed day after chloroform; found dead on second day
52 (Dog 19-13)	4	Strychnin sulph. on 2 days preceding chloroform	1	2/3 to 3/4	2/5; heavy	Piece of liver removed on second day; found dead on third day
53 (Dog 19-18)	3	Toxic proteose intravenously during chloroform	1 1/4	4/5	Slight to periphery	Died in less than 24 hours
54 (Dog 19-87)	0	Toxic proteose intravenously during chloroform	1 1/4	0	0	Dog had distemper; not on starvation, but had poor appetite; operated on second day; liver shows cloudy swelling; recovered

3. Graham, E. A.: *J. Exper. M.* 21:185, 1915.4. Pavy, F. W., and Bywaters, H. W.: *J. Physiol.* 41:168, 1910-1911.5. Pavy, F. W., and Godden, W.: *J. Physiol.* 43:7, 1911-1912.6. Underhill, F. P.: *J. Biol. Chem.* 25:463, 1916. McDanell, Louise, and Underhill, F. P.: *J. Biol. Chem.* 29:227, 251 and 265, 1917.

EXPERIMENT 48.—*Epinephrin Injections Previous to Chloroform Anesthesia.*—Dog 19-4, a young, female terrier.

Aug. 12: Wt., 19.3 lbs. Isolated for starvation before daily feeding; healthy and very active.

Aug. 13: Very active; 7 c.c. epinephrin (epinephrin chlorid 1:1,000) intramuscularly at 11 a. m.; 3.5 c.c. epinephrin intramuscularly at 4:30 p. m.

Aug. 14: Wt., 18.63 lbs. Weak in hind limbs. Four c.c. epinephrin subcutaneously at 9 a. m.; 7.5 c.c. epinephrin intramuscularly at 4:30 p. m.

Aug. 15: Wt., 17.63 lbs. Left hind leg extremely swollen, and cannot be used. *Chloroform for one and a quarter hours* (from 8:50 to 10:05 a. m.).

Aug. 16: Wt., 17.25 lbs. Leg much better; bright, but not active.

Aug. 17: Wt., 17.25 lbs. Abscess opening on left thigh. Piece of liver removed at 10 a. m. Sections show a mere trace of central necrosis, a few large vacuolated cells, and a scattering of small fat droplets over about two fifths of each lobule.

EXPERIMENT 49.—*Epinephrin Injection Shortly Before Chloroform Anesthesia.*—Dog 19-73, a black and tan male terrier.

Nov. 15: Wt., 17.56 lbs. Isolated before daily feeding; *starvation*. Dog is young and immature; very active.

Nov. 16: Wt., 17 lbs. Nov. 17, *starvation*; very active.

Nov. 18: Wt., 16.3 lbs. Active; in good condition; 7.5 c.c. of epinephrin (epinephrin chlorid 1:1,000) subcutaneously at 11:45 a. m. *Chloroform for one and a quarter hours* (from 1:10 to 2:25 p. m.). At time of anesthesia the pupils were still greatly dilated, but the pulse was back to normal.

Nov. 19: Wt., 16.2 lbs. Quiet and a little dull; weak in hind limbs; beef extract diet.

Nov. 20: Wt., 15.56 lbs. Becoming toxic; vomited; sacrificed at 3:30 p. m.

Necropsy Report.—Tissue of left side of body from thigh to axilla, is necrotic in places. (Result of subcutaneous injection of epinephrin.) Viscera pale from exsanguination. *Liver*: apparently about one half fatty; necrosis does not show in gross.

Microscopic Report.—*Liver*: a strong one half necrotic, with fat in necrotic areas. *Spleen*: slightly congested.

EXPERIMENT 50.—*Quinin Sulphate Previous to Chloroform Anesthesia.*—Dog 18-124, a young, black and white female.

Nov. 4: Wt., 13.3 lbs. Isolated for starvation before daily feeding. Operative incisions of other operations healed. Gave 1 gm. *quinin sulphate* in weak acid by stomach tube; frothy vomitus later. (Weak acid = 50 c.c. H₂O + 8 drops conc. H₂SO₄.)

Nov. 5: Wt., 12.75 lbs.; 1 gm. *quinin sulphate* in weak acid by stomach tube; became weak and unsteady; frothy vomitus.

Nov. 6: Wt., 12.2 lbs.; 1 gm. *quinin sulphate*; reaction as before.

Nov. 7: Wt., 11.63 lbs.; 1 gm. *quinin sulphate*; reaction as before. *Chloroform for one and a quarter hours* (from 3:05 to 4:20 p. m.).

Nov. 8: Wt., 11.3 lbs. Quite active; mixed food.

Nov. 9: Wt., 11.9 lbs. Sacrificed at 10:30 a. m.

Necropsy Report.—Abdominal wounds are healed superficially, but show stitch abscesses in the deeper parts; mediastinal lymph nodes large and dark; viscera pale from exsanguination. *Spleen*: somewhat shrunk and firm. *Liver*: shows small stitch abscesses and extreme fibrosis at operative sutures; parenchyma shows red lobule centers—suggesting necrosis—and pale, opaque areas.

Microscopic Report.—*Liver*: central engorgement: practically no necrosis: severe injury (large vacuolated cells, and a trace of fat) in central one third to two fifths. *Kidney*: cells of cortex very much swollen. *Spleen*: engorged.

EXPERIMENT 51.—*Starvation (Control).*—Dog 19-11, a brown mongrel male pup.

Aug. 5: Wt., 11.8 lbs. Isolated before daily feeding; *starvation*; healthy and very active.

Aug. 6 to 7: *No food*; very active and noisy.

Aug. 8: Wt., 10.8 lbs. Healthy and active. *Chloroform* for one hour (from 12:50 to 1:50).

Aug. 9: Wt., 10.5 lbs. Quiet; developing distemper.

Aug. 10: Found dead.

Necropsy Report.—*Lungs*: show extensive, diffuse, bronchopneumonia, with hemorrhage, especially noticeable in lower lobes. *Liver*: weight 212 gm.; lobule centers are dark red, surrounded by a narrow zone of opaque, yellowish-white tissue. *Spleen*: shows some dark purplish patches, perhaps postmortem. *Stomach* contains a few flecks of old blood; definite hemorrhagic foci not found.

Microscopic Report.—*Liver*: two thirds to three quarters coagulative necrosis; heavy deposits of fat to periphery of lobules. *Kidney*: some cloudy swelling.

EXPERIMENT 52.—*Strychnin Sulphate Precious to Chloroform Anesthesia.*—Dog 19-13, a young female terrier.

Aug. 5: Wt., 14.56 lbs. Isolated before daily feeding; *starvation*; healthy and active.

Aug. 6: *No food*; 2.5 gm. *strychnin sulphate* subcutaneously at 12 m.

Aug. 7: Wt., 13.63 lbs. *No food*; 3.25 mg. *strychnin sulphate* at 5:15 p. m.

Aug. 8: Wt., 13.38 lbs. Apparently as well as usual. *Chloroform* for one hour (from 8:50 to 9:50 a. m.).

Aug. 9: Wt., 12.63 lbs. Quiet and a little dull.

Aug. 10: Wt., 12.75 lbs. Droopy. *Piece of liver removed* at 12 m.; left food in cage.

Aug. 11: Found dead.

Necropsy Report.—Body still warm; rigor mortis beginning; heart blood not clotted, but forms flabby clots slowly on contact with tissues; some free blood in peritoneal cavity, but not enough to account for death in itself; good clot over liver wound. *Liver*: weight 208 gm.; necrosis and fat very evident. *Thymus*, dark, probably hemorrhagic. *Pancreas* quite dark. *Spleen* and *kidneys* normal in gross.

Microscopic Report.—Operation and necropsy show much the same picture in the *liver*; two thirds to three quarters hyaline coagulative necrosis; fine scattering of fat through necrosis, and heavy from edge to lobule periphery. *Thymus* engorged. *Kidney*: some cloudy swelling.

EXPERIMENT 53.—*Proteose Intravenously During Chloroform Anesthesia.*—Dog 19-18. Old male mongrel.

Aug. 14: Wt., 17 lbs. Isolated after daily feeding; active and healthy.

Aug. 15 to 16: Fasting.

Aug. 17: Wt., 15.7 lbs. *Chloroform* for one and a quarter hours (from 8 to 9:15 a. m.); 35 c.c. *toxic proteose solution* (mixture from three experimental obstruction dogs); 200 c.c. normal saline intravenously during the first hour of anesthesia; vomited bile within an hour; very dull; bad pulse; salivation; mere trace of phenolsulphonephthalein output.

Aug. 18: Found dead.

Necropsy Report.—Blood well clotted. *Thymus* remnant hemorrhagic. *Liver*: weight 332 gm.; extremely swollen and congested, with many hemorrhages; mucosa of *duodenum* very hemorrhagic; blood in lumen of gut farther down; autodigestion throughout. *Kidneys*: slightly full and hyperemic.

Microscopic Report.—*Liver*: about four fifths hemorrhagic necrosis, with heavy pigmentation, and trace of fat to lobule peripheries. *Lungs*: hemorrhage. *Kidney*: cloudy swelling and destruction of parenchyma. *Spleen*: congestion and pigmentation.

Drummond and Paton,⁷ and others, have reported a diminished liver glycogen in acute epinephrin poisoning. No doubt the well known hyperglycemia and glycosuria has lent support to this work. Kuriyama⁸ has recently published work on "The Adrenals in Relation to Carbohydrate Metabolism" in which he shows by liver analyses that starved rabbits given epinephrin have more liver glycogen than the controls. Subcutaneous injections caused an increase, sometimes of a thousand per cent. over the controls, in spite of the glycosuria. Even one dose of 1 mg. per kilo body weight given ten hours before sacrifice caused a marked increase over the control animal. Whipple and Christman⁹ have shown that adrenal insufficiency causes a fall in phenoltetrachlorophthalein output in the bile.

Dog 19-10 in Experiment 47 shows a marked protection from two injections of epinephrin chlorid (see Control Experiment 51). The protection is still more noticeable in Experiment 48 from four injections. One dog was lost because too large a dose of epinephrin was given intravenously during chloroform anesthesia. Experiment 49 shows the effect of giving epinephrin shortly before the chloroform. In this case little, if any protection is demonstrable.

While these experiments were undertaken on the strength of Kuriyama's work, with the hope of showing a greater protection than in controls because of a difference in liver glycogen, we do not feel that any definite proof is furnished even though the results are clear cut. If all our feeding experiments pointed in the same direction, this would be corroboratory evidence for the influence of glycogen. Whatever the protective action of epinephrin may be, it seems to require time to develop, and is not an immediate effect of the drug.

Quinin sulphate is a drug supposed to decrease body metabolism;¹⁰ probably in connection with this power, it favors the preservation of liver glycogen. Lepine and Porteret¹¹ found that guinea-pigs given quinin had 20 per cent. more liver glycogen than the controls. Nebelthau¹² corroborated these observations.

7. Drummond, W. B., and Paton, D. N.: J. Physiol. **21**:92, 1904.

8. Kuriyama, S.: J. Biol. Chem. **24**:269, 1918.

9. Whipple, G. H., and Christman, P. W.: J. Exper. M. **20**:297, 1914.

10. Sollmann, T.: A Manual of Pharmacology, W. B. Saunders Co., 1917, p. 455.

11. Lepine and Porteret: Compt. rend. de l'acad. de sc. **106**:1023, 1888. Cited by Salant, W.: Studies from the Rockefeller Institute for Medical Research **8**: 1908.

12. Nebelthau: Ztschr. f. Biol. **28**:138, 1891. Cited by Salant, W.: Studies from the Rockefeller Institute for Medical Research **8**: 1908.

Experiment 50 shows the protection afforded by quinin sulphate. Dog 18-124 had previously sustained an injury of $\frac{1}{2}$ necrosis resulting from chloroform following starvation alone (see Experiment 23); the contrast in injury is very striking. Here again the evidence is in harmony with a glycogen protective theory.

Strychnin sulphate is a substance one of whose pharmacologic actions is supposed to be the reduction of liver glycogen. Experiment 53 shows the effect of giving relatively large doses on the two days

TABLE 9.—POTASSIUM CYANID, OR HYDRAZIN SULPHATE IN ADDITION TO CHLOROFORM ANESTHESIA

Experiment	Starvation, Days	Supplementary Treatment	Chloroform, Hours	Liver Injury		Remarks
				Central Necrosis	Fat	
55 (Dog 19-54)	4	Potassium cyanid intravenously; ether anesthesia (control)	0	0	Heavy throughout	Died from distemper pneumonia on second day
56 (Dog 19-57)	0	Potassium cyanid intravenously; ether anesthesia	0	0	Moderate throughout	Distemper dog; toxie after injection; operation on third day
	4	Starvation only (control)	$1\frac{1}{4}$	$\frac{3}{5}$	Slight, diffuse throughout	Operation on second day; dog died about 2 weeks later from combined effects of chloroform injury, operation and distemper
57 (Dog 19-81) Pup	0	Potassium cyanid intravenously during chloroform anesthesia	1	?	0	Brain diet for 4 days; previously showed no injury from chloroform alone after brain diet (see Exper. 12). Prostrated; died less than 5 hours after chloroform; central cells show granular degeneration
58 (Dog 19-80) Pup	3	Potassium cyanid intravenously during chloroform anesthesia	1	$\frac{1}{4}$	Trace	Not able to push the anesthesia on account of bad pulse and respiration; operation on second day
59 (Dog 19-87)	0	Potassium cyanid intravenously during chloroform anesthesia	$1\frac{1}{4}$	$\frac{1}{2}$	Heavy in necrosis	Distemper dog; poor appetite (see Exper. 54). Cells surrounding necrosis are vacuolated; sacrificed on second day; low fibrin
60 (Dog 19-53)	4	375 mg. hydrazin sulphate subcutaneously (control)	0	0	Very intense throughout	Toxie; dead on second day; weighed 10.8 lbs. at time of injection
61 (Dog 19-59)	3	400 mg. hydrazin sulphate subcutaneously (control)	0	0	$\frac{1}{2}$; moderate	Quite sick; dead on second day; complicated by distemper and developing pneumonia; weight 17.5 lbs. at time of injection
62 (Dog 19-12)	4	240 mg. hydrazin sulphate subcutaneously on day preceding chloroform	1	Trace	Very intense throughout	Young, immature dog; toxie; distemper developed following chloroform; sacrificed; weight 16.5 lbs. at time of injection (see control, Ex. 51)

preceding chloroform anesthesia. The resulting injury is maximal under the conditions of starvation and chloroform, as is that in the case of Control Experiment 51. Dog 19-13, however, was somewhat older than Dog 19-11, and if maturity is a recognizable protection, perhaps the dog receiving strychnin may be considered to have received a slightly greater injury.

Experiments 53 and 54 were performed with a mixture of "toxic proteose" from three experimentally obstructed dogs. Such material is known to increase bodily catabolism, and from clinical observations probably interferes with oxidative processes. Dog 19-18 was given a dose which later work showed might have been fatal in itself, and in addition was given an hour and a quarter chloroform anesthesia. The result was great prostration, and death in less than twenty-four hours. The necropsy picture was that of proteose intoxication, but further, the liver showed four-fifths necrosis, which one certainly would not expect from the chloroform alone, after only three days' starvation. Dog 19-87 had not been starved, although eating poorly on account of distemper, and received a sublethal dose of proteose; the chloroform apparently caused very little injury.

EXPERIMENT 55.—*Cyanid Intravenously; No Chloroform (Control).*—Dog 19-54, a black and brown female mongrel.

Oct. 18: Wt., 17.38 lbs. Isolated for *starvation*; distemper severe; appetite poor.

Oct. 19 to 20: Starvation.

Oct. 21: Wt., 16 lbs.; 15 mg. KCN in 200 c.c. 0.9 per cent. NaCl intravenously during about one-half hour of ether anesthesia; preliminary increase in respiration followed by apnea, then shallow, slow breathing; apparently unconscious without ether; bounding pulse became flabby by end of injection; recovered from effects in about one hour; full diet.

Oct. 23: Found dead.

Necropsy Report.—Fibrino-purulent pleurisy, bronchopneumonia and pericarditis; liver looks orange-yellow—probably fatty.

Microscopic Report.—*Liver:* fat heavy throughout; engorged with blood; practically no necrosis. *Lungs:* extreme grade of pneumonia; no fibrin. *Kidneys:* cloudy swelling.

EXPERIMENT 56.—*Cyanid Intravenously; No Chloroform (Control).*—Dog 19-57, an old male collie.

Oct. 25: Wt., 63 lbs. Distemper dog; gave 53 mg. KCN in 300 c.c. saline intravenously.

Oct. 26 to 27: Eats some, but appears sick.

Oct. 28: *Piece of liver removed* at 1:45. Sections show no necrosis, but a moderate sprinkling of finely divided fat throughout.

EXPERIMENT 56.—*Chloroform Only.*—Dog 19-57, an old male collie.

Nov. 10: Wt., 60.9 lbs. Isolated for starvation; distemper practically disappeared; abdominal wound healed.

Nov. 11 to 12: No food.

Nov. 13: Wt., 57.6 lbs. Distemper flaring up again. *Chloroform* for one and a quarter hours (from 10 to 11:15 a. m.).

Nov. 15: Piece of liver removed at 1:30; considerable hemorrhage; sections show three fifths necrosis; fat slight, diffuse throughout. Dog died in about two weeks from combined effects of chloroform injury, operation and distemper.

EXPERIMENT 58.—*Potassium Cyanid Intravenously During Chloroform.*—Dog 19-89, a spotted female pup.

Dec 16: Isolated before daily feeding; starvation.

Dec. 17: Wt., 8.38 lbs. Bright and active; no food.

Dec. 18: Wt., 7.96 lbs. Bright and active; no food. *Chloroform for one hour* (from 10:20 to 11:20 a. m.). Gave 4 mg. KCN in 100 c.c. saline intravenously during three-quarters hour of anesthesia; could not push the anesthetic on account of bad pulse and respiration.

Dec. 17: Mixed diet.

Dec. 20: Wt., 8 lbs. *Piece of liver removed at 1:30.* Sections show a moderate injury; about one fourth necrosis, not at all uniform; a mere trace of fat.

Jan. 3: Died from distemper pneumonia.

EXPERIMENT 59.—*Potassium Cyanid Intravenously During Chloroform.*—Dog 19-87, a black and white female terrier.

Dec. 30: Wt., 12 lbs. Isolated; distemper very bad; abdominal wound (from previous operation) superficially open; eats very little. *Chloroform for one and a quarter hours* in a. m. Gave 8 mg. KCN in 160 c.c. physiologic sodium chlorid solution at intervals during anesthesia; was able to use chloroform quite freely.

Dec. 31: Dull; poor appetite.

Jan. 1, 1919: *Sacrificed* in a. m.; fibrin less than 100 mg. per 100 c.c. plasma.

Necropsy Report.—Viscera all pale from exsanguination; mediastinal lymph nodes hyperemic. *Liver* is orange-colored; lobule centers are prominent—probable necrosis. *Spleen* is small and fibrous. *Kidneys* are very flabby.

Microscopic Report.—*Liver:* approximately one half necrosis; fat in quite heavy deposits throughout the necrosis; cells in immediately surrounding zone are vacuolated considerably. *Kidneys:* slight cloudy swelling; abscess in medulla.

EXPERIMENT 61.—*Hydrazin Sulphate Only (Control).*—Dog 19-59, a mongrel male bull.

Oct. 26: Isolated for starvation; distemper rather bad; mean tempered.

Oct. 27: No food.

Oct. 28: Wt., 17.5 lbs. Gave 400 mg hydrazin sulphate subcutaneously.

Oct. 29: Wt., 16.13 lbs. Quite sick.

Oct. 30: Found dead.

Necropsy Report.—Severe bronchitis and some pneumonia in left lung; blood clots all right. *Liver* and *spleen* quite engorged; probably a certain amount of diffuse fat in liver, but it does not show up very well. *Kidneys:* pale, suggesting fat.

Microscopic Report.—*Lung:* some pneumonia. *Spleen:* engorgement; pigment. *Liver:* central engorgement; pigment, especially in Kupfer cells; moderate amount of fat in central one half of lobules. *Kidneys:* cloudy swelling.

EXPERIMENT 62.—*Hydrazin Sulphate Previous to Chloroform.*—Dog 19-12, a black, half-grown male mongrel.

Aug. 5: Wt., 17.5 lbs. Isolated before daily feeding; *starvation*; in good condition; active.

Aug. 6: No food.

Aug. 7: Wt., 16.5 lbs. No food; 240 mg. hydrazin sulphate subcutaneously.

Aug. 8: Wt., 15 lbs. Quite dull. *Chloroform for one hour* (from 12:50 to 1:50).

Aug. 9: Wt., 15.2 lbs. Sick and droopy.

Aug. 10: Wt., 15.25 lbs. Beginning distemper; *sacrificed* in a. m.; blood urea, 20 mg.; urea N, 9 mg.

Necropsy Report.—*Liver* is extremely fatty; necrosis is not striking, although lobule centers generally show a dot orange to red in color; there is one spot of subcapsular hemorrhage 0.5 by 1 cm. near the hilum; other organs negative.

Microscopic Report.—*Liver*: about four fifths severely injured; small patches of frank necrosis; heavy deposits of fat to lobule peripheries.

In an article published in 1912, Graham¹³ makes the statement that chloroform is one of a group whose effect on organs is like that of asphyxiation. He has later amplified this statement with the suggestion that many common anesthetic substances, including chloroform and ether, also carbon monoxid and potassium cyanid, are capable of dissociating in a manner which yields bivalent or unsaturated carbon. It is easy to imagine that such compounds might then appropriate oxygen within the body, in order to satisfy their free bonds.

Wells¹⁴ has suggested that chloroform may unite with the cell lipoids, perhaps physically, then poison the protoplasm, probably by interfering with oxidative and synthetic functions. Autolysis is not hindered, and the lipase continues its activity without the resulting products being oxidized; hence the fatty liver. Lactic acid is increased, which may possibly be correlated with the observation of Macleod and Wedd¹⁵ that lactic acid is much increased in the hepatic blood if the liver oxygen supply is cut down, for instance, by temporarily clamping the hepatic artery and portal vein. Disintegration products accumulate and become toxic, aided by the impaired function of liver and kidneys. Whipple¹⁶ has shown by the phenoltetrachlorophthalein liver test that in severe chloroform poisoning, the liver function goes down almost to zero.

Whipple¹⁷ found that in moderate or severe chloroform injury the blood lipase is considerably above normal. Quinan¹⁸ found that the liver lipase (or esterase) in such injuries may be decreased as much as 38 per cent. Jobling, Eggstein and Peterson¹⁹ confirmed the observations of both Whipple and Quinan, but maintain that the increase in serum lipase is not liberated by the disintegrating liver cells, since the blood of the hepatic veins has a poorer content than the blood

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14. Wells, H. G.: J. A. M. A. **46**:341, 1906; Arch. Int. Med. **1**:589, 1908; Chemical Pathology, W. B. Saunders Co., 1918, Ed. 3.

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16. Whipple, G. H., and Speed, J. S.: J. Exper. M. **21**:203, 1915.

17. Whipple, G. H.: Bull. Johns Hopkins Hosp. **24**:1, 1913.

18. Quinan, C.: J. M. Res. **32**:73, 1915.

19. Jobling, J. W., Eggstein, A. A., and Peterson, W.: J. Exper. M. **22**:707, 1915.

elsewhere. Very recently Simonds²⁰ claims to have shown that neither the esterase nor the ereptase of the liver is appreciably affected by chloroform poisoning. Opie, Barker and Dochez²¹ have shown that after chloroform or phosphorus poisoning, there is an increase in anti-enzyme (in the blood) for those enzymes active in alkaline mediums, perhaps compensatory to the liberation of the latter from the breaking down liver cells, and that the proteolytic enzyme of the blood stream which acts in an acid medium is increased in such conditions, perhaps, also, liberated from the liver; this last enzyme is held in check by the alkalinity of the blood.

Burge²² has found that narcotics decrease the oxidative enzyme, catalase, in the blood stream, and believes that narcosis is due to decreased oxidation, following destruction of catalase in the nervous system. Consequent to the administration of chloroform, catalase drops 42 per cent. in fifteen minutes, while ether reduces catalase about 9 per cent. in the same length of time. At the end of one and one-half hours, however, the percentage reduction is more nearly the same, that from chloroform being 65 per cent., and that from ether 54 per cent. Burge's theory is that catalase is formed to a large extent in the liver, but some in the intestines, spleen, pancreas, etc. He thinks that oxidation controls autolysis, perhaps by oxidizing the autolytic enzymes under normal conditions. Ingestion of food increases the catalase of the blood and tissues parallel with the increase in heat production; the increase is due to stimulation of the liver by digestion products. Burge's work on narcotics supports the position of Verworn.²³

Loeb and Wasteneys²⁴ have found a maximum reduction in oxidation of 20 per cent. in testing a number of narcotics, chloroform among the group; this they showed to be insufficient to produce asphyxiation.

Loevenhart²⁵ and his co-workers have done some very interesting work with cyanids and organic peroxids, such as iodoso- and iodoxybenzoic acids and their sodium salts. They find that, injected intravenously, cyanid intensifies, and the peroxids diminish inflammatory

20. Simonds, J. P.: *J. Exper. M.* **28**:663, 673, 1918.

21. Opie, E. L., Barker, B. I., and Dochez, A. R.: *J. Exper. M.* **13**:162, 1911.

22. Burge, W. E.: *Am. J. Physiol.* **43**:545, 1917; *Science* **46**:618, 1917; *J. Pharm. and Exper. Therap.* **12**: (Nov.) 1918. Burge, W. E., and Neill, A. J.: *Am. J. Physiol.* **43**:58, 1917; *Ibid.* **46**:117, 1918; *Ibid.* **47**:13, 1918. Burge, W. E., Neill, A. J., and Ashman, R.: *Am. J. Physiol.* **45**:388, 500, 1918.

23. Verworn, Max: *Harvey Lectures* **7**: 1911-1912.

24. Loeb, J., and Wasteneys, H.: *J. Biol. Chem.* **14**:517, 1913.

25. Loevenhart, A. S., and Grove, W. E.: *J. Pharm. and Exper. Therap.* **1**:289, 1909-1910; *Ibid.* **3**:101, 131, 1911-1912. Amberg, S., and Knox, J. H. M.: *J. Pharm. and Exper. Therap.* **3**:223, 1911-1912. Amberg, S., Loevenhart, A. S., and McClure, W. B.: *J. Pharm. and Exper. Therap.* **10**: (Sept.) 1917.

processes, such as the mustard oil reaction, and the intracutaneous reaction in serum sensitization. These results seem to be due to the effect on bodily oxidations and reductions. Furthermore, these workers²⁶ were able to produce central necrosis in rabbits' livers by suboxidation, the animals being left in an atmosphere of low oxygen tension for several days at a time.

It occurred to us that if chloroform causes liver injury primarily because it reduces oxidation, a substance such as potassium cyanid, whose action in that direction is well known, might intensify the effect of chloroform administration.

Experiment 55 indicates the result of injecting intravenously 1 mg. per pound body weight of potassium cyanid during ether anesthesia. The dosage caused quite severe prostration, but the liver two days later showed only fatty changes. Experiment 56 shows the comparative liver injury from 0.83 mg. potassium cyanid per pound body weight, and from one and one-fourth hours chloroform anesthesia following starvation. Here again the cyanid caused only fatty alterations, while chloroform gave the usual picture of severe necrosis.

Dog 19-81 (Experiment 57) had previously shown no liver necrosis from one hour's chloroform anesthesia following brain diet. In Experiment 57 this same dog received brain diet again, but at time of anesthesia received 1 mg. per pound body weight of potassium cyanid in addition to the chloroform. The pup never regained consciousness, and died about five hours later. The central cells ($\frac{2}{3}$) in the liver lobules look somewhat granular, and stained lighter than the peripheries; this picture was also seen after the chloroform alone, following brain diet. Manifestly, five hours is rather too soon after injury for chloroform necrosis to show clearly. Some of this liver tissue autolyzed in saline at body heat for six and one-half hours, also some left at room temperature over night, showed a greater tendency toward autolysis in the centers of the liver lobules. This experiment is unsatisfactory in many respects, but the action of potassium cyanid on the liver is not very marked.

In Experiment 58 the pup received only 0.5 mg. per pound body weight in addition to the chloroform anesthesia. The resulting necrosis is below the average for a pup starved three days and given one hour of chloroform anesthesia. Probably the pup did not receive quite as much chloroform as would have been the case had the cyanid not affected the pulse and respiration. The effect of the cyanid is not manifest.

26. Martin, G. H., Bunting, C. H., and Loevenhart, A. S.: *J. Pharm. and Exper. Therap.*, Proc. 8:112, 1916.

Dog 19-87 (Experiment 59) received $\frac{2}{3}$ mg. cyanid per pound body weight in addition to one and one-fourth hours of chloroform anesthesia. Little trouble was had in administering the anesthetic in this case. The injury is greater than is to be expected in a fed animal from giving such an amount of chloroform; however, this dog had been suffering from severe distemper for some time, and under such conditions very little food is ever consumed; hence this dog was in an undernourished state approximating starvation, and a marked necrosis was to be expected. That the potassium cyanid influenced the amount of necrosis may be doubted.

Wells²⁷ has reported on the pathology of *hydrazin poisoning*; one of the most important findings is a more or less severe fatty degeneration of the liver. Underhill²⁸ and his co-workers have published a long series of papers dealing with the physiologic disturbances caused by hydrazin. Among other things, there is a marked hypoglycemia, and the glycogen content of the liver and muscles is reduced practically to zero. No specific influence is noticed on heat production, but the respiratory quotient shows an increased carbohydrate metabolism. Apparently the glyoxalase activity of the liver is not greatly altered by hydrazin. The blood fats are considerably increased, the maximum rise being coincident with the hypoglycemia.

In Experiments 60 and 61 hydrazin sulphate was given subcutaneously, and the liver injury was determined on the second day. Both dogs died; in Experiment 60, at least, death was undoubtedly due to hydrazin. In Experiment 62 a relatively small dose of hydrazin was given and one hour of chloroform anesthesia as is usually administered to pups. The fatty picture is comparable to that in Experiment 60, in which over twice as much hydrazin sulphate was given per pound body weight. It is noticeable that Dog 19-59 (Experiment 61) was nearly the same weight as Dog 19-12 (Experiment 62) and received much more hydrazin per pound, yet showed very much less fat. It may be concluded that the fatty picture in Experiment 62 could not have been caused by either the hydrazin or the chloroform alone. The small amount of frank necrosis is very striking. This phenomenon is hard to explain; Control Experiment 51 shows severe necrosis following starvation and chloroform anesthesia; if lack of liver glycogen predisposes to chloroform injury, Dog 19-12 should certainly reveal a marked necrosis, while as a matter of fact there is very little present.

27. Wells, H. G.: J. Exper. M. **10**:457, 1908.

28. Underhill, F. P., and Kleiner, I. S.: J. Biol. Chem. **4**:165, 1908. Underhill, F. P.: J. Biol. Chem. **10**:159, 271, 1911-1912; **17**:293, 1914. Underhill, F. P., and Hogan, A. J.: J. Biol. Chem. **20**:203, 211, 1915. Underhill, F. P., and Martin, J. R.: J. Biol. Chem. **22**:499, 1915.

GENERAL DISCUSSION

The experiments reported in this paper naturally fall into three groups. The first group contains the experiments designed to repeat Graham's work on the protective action of carbonate solution against chloroform injury. Under carefully controlled conditions we cannot corroborate Graham's findings.

The second set of experiments was undertaken with the hope of sparing or diminishing the liver glycogen by means of drugs, to see whether such reactions affected the subsequent chloroform liver injury. Here the evidence is more or less contradictory; the epinephrin and quinin treatments fulfilled the requirements for which they were chosen, in so far as injury was lessened; whether this effect was a result of increased liver glycogen was not determined. Strychnin, supposed to lessen the liver glycogen content, did not cause any marked increase in chloroform injury. Hydrazin sulphate, also known to lessen liver glycogen content, caused an increase in fatty degeneration, but actually appeared to lessen necrosis. The status of liver glycogen in relation to chloroform liver injury is not settled as a result of these experiments.

The third group of experiments was designed to obtain evidence concerning the relation of bodily oxidations to chloroform liver necrosis. It would appear that large doses of "toxic proteose" intensify the injury, while small doses have no effect. Potassium cyanid has a very prostrating immediate effect, but seems to have very little influence on delayed liver injury and necrosis. The results of these experiments are hard to reconcile with a theory of chloroform necrosis due to lowered oxidation.

Although chloroform is losing favor as an anesthetic, it is still employed extensively by some physicians. In view of the frequent therapeutic use of such drugs as epinephrin and quinin it may be well to call attention to a possible practical value of these drugs. In cases of pernicious vomiting, for example, it would be very dangerous to use chloroform because of the starved tissues, but it might be possible to lessen the probable liver injury by means of the drugs mentioned.

SUMMARY

Sodium carbonate in hypertonic salt solution given intravenously during chloroform anesthesia has no protective action against the resultant liver injury.

Phosphate solutions, high in buffer content, have no protective action against chloroform liver injury.

Epinephrin subcutaneously or intramuscularly in the days preceding chloroform anesthesia exerts a distinct protective action against

chloroform liver injury. The resistance requires time to develop, and is not demonstrable by a single dose of epinephrin a short time before chloroform administration.

Quinin sulphate given in the days preceding chloroform exerts a marked protective action against liver injury.

Hydrazin sulphate, although itself injurious to the liver, apparently does not intensify (perhaps lessens) the toxic action of chloroform.

It would appear that strychnin sulphate has very little deleterious action on an ordinary chloroform injury following starvation.

Toxic proteose solutions in large dosage may intensify the chloroform injury, but in small amount seems to have no effect.

Potassium cyanid given intravenously during chloroform anesthesia, although very toxic at the time, seems to exert little, if any, influence on the delayed chloroform poisoning (liver injury).

The hypothesis that glycogen protects the liver cell against the injury of chloroform will not explain all the observed facts. Some of our experiments are in harmony with this hypothesis, but others are equally positive against it. This simple explanation of the resistance of liver cells to chloroform injury does not suffice, and undoubtedly other factors are concerned which must be searched out.

The hypothesis that chloroform injury and liver necrosis is to be explained by a lowering of the level of tissue oxidation (tissue asphyxia) receives no support from our experiments.

The peculiar protective action of epinephrin and quinin sulphate in chloroform poisoning may have some practical clinical application.

BOOK REVIEW

RADIO-DIAGNOSIS OF PLEURO-PULMONARY AFFECTIONS. By F. Barjon. Translated by James A. Honeij, M.D., Assistant Professor of Medicine in Charge of Radiography, Yale Medical School. Cloth. Price, \$2.50. Pp. 183, with illustrations. New Haven: Yale University Press, 1918.

The roentgen-ray examination of the lungs has become an indispensable clinical method. It is astonishing how rapidly it has forced a way to an acknowledged position beside more time-honored methods. But on account of this rapid advance it has been difficult to keep pace with its progress. Some have greeted it with the indifference and suspicion always accorded a parvenu; others have acclaimed it with the exaggerated enthusiasm always bestowed on a new and brilliant arrival. Between the indifferent and the partisan, it has usually been either too coolly or too warmly received. Only a few sober minds have paused to weigh critically its pretensions and to guide it to the place justly deserved. There is great need at present that some one properly endowed should present these pretensions in a warm but unbiased way, so that the method may be saved from the extravagance of its overzealous friends and still receive proper recognition. Here is a work from a skilled technician and a physician of wide experience and rare judgment. Barjon's book is an attempt to meet this need. It is the most meritorious contribution to the subject that has yet appeared, although it falls far short of the desired treatise. It is too sketchy, too brief, too provincial. A few French authors are cited, but otherwise the whole mass of valuable material contributed by numerous investigators is completely ignored. In spite of these shortcomings, however, the book may be recommended as a concise and satisfactory guide to the subject.

Unfortunately, the author is introduced to his American audience in an unattractive garb. The translation is no doubt faithful, but the French idiom is preserved, and the language is not only unattractive but in some places difficult to interpret.

THE INFLUENZA EPIDEMIC OF 1918 IN THE AMERICAN EXPEDITIONARY FORCES IN FRANCE AND ENGLAND

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INTRODUCTION

In the spring of 1918 reports appeared of an epidemic disease in various parts of Southern France, Italy and Spain. Greater publicity was given to these reports in Spain, doubtless, in part, because that country was not engaged in war. By midsummer this disease had spread widely throughout Europe, and in the autumn had involved South Africa and America.

Numerous reports dealing with outbreaks of this disease have accumulated in the office of the Chief Surgeon, A. E. F., and in several instances special investigations of the epidemiology and bacteriology of these outbreaks have been reported. The purpose of the present paper is to give a summary account of the disease in the A. E. F., based on these reports, and to bring the observations made here into correlation with reports of the disease elsewhere. Manifestly, available reports are in many instances fragmentary, and the world's literature is not at hand for consultation, even if the necessary time could be devoted to it. Especially unsatisfactory are the reports of the disease in the military and civilian population of the belligerent countries, reports which one reads always with a suspicion that scientific accuracy may have been sacrificed to military or political considerations. It is intended to present here the known facts in regard to the disease, without regard to censorship, and it is expected that this paper will not receive publicity until the necessity for military or political censorship shall have ceased to exist. It may then become possible to obtain a sufficient number of reports from different countries so as to obtain a broad view of this pandemic and perhaps to arrive at clear and definite conclusions in regard to features now obscure.

CLINICAL MANIFESTATIONS

General Considerations.—The clinical signs and symptoms of the disease are not entirely uniform and are similar to the manifestations of the group of acute infectious fevers. Were it not for the epidemi-

ologic evidence it would be difficult to characterize the disease as a distinct and definite clinical entity. Nevertheless, when it appears in the epidemic form, the early signs and symptoms are strikingly similar. At such times the most common and dangerous mistake is the designation of early cerebrospinal fever and of various respiratory infections as influenza because of the existence of an epidemic of the latter disease.

Onset.—In the majority of cases, the beginning of the disease has been sudden, particularly in the warmer season. For example, a man would go to bed feeling entirely well, would awaken in the night with a severe headache, followed soon by pain in the back, general malaise and fever. In other instances, the man suddenly became aware of headache, weakness and pains in the somatic muscles while on duty or on attempting some bodily exertion. Epistaxis has been an early manifestation in a considerable proportion of cases. Anorrexia, more or less complete, has been usual at the onset and nausea and vomiting have occurred in a small proportion. In some outbreaks, particularly those in the later months, a slight sore throat or a feeling of cold in the head, and in some instances a distinctly localized burning sensation in the nasopharynx was noticed twelve to twenty-four hours before the fever became evident. In a certain proportion of the cases, the onset would appear to have a relation to bodily exertion or fatigue, such as guard duty, standing at inspection, or a long march. In officers the onset has been observed after delivering lectures of instruction as well as other fatiguing duties.

The onset symptoms, although in most instances severe enough to fix the moment of onset in the patient's mind, have, as a rule, been mild enough so that soldiers would not report sick unless especially ordered to do so. The morale of the average soldier has been such that he has hesitated to go to sick call, regarding it as a confession of weakness or perhaps an indication that he desired to shirk. While this attitude is, in general, to be commended, and has undoubtedly been encouraged by medical officers, it has been a distinct source of danger in the presence of this epidemic. The failure to detect early cases has cost many lives, and the practice of encouraging immediate report at the first sign of illness has become an important feature in the control of the disease. In the presence of an epidemic it has been found wise for the medical officer to inspect every man of his organization every afternoon, to examine all who appeared ill and to transfer to hospital all with a temperature above 99.5 F. In a considerable proportion of cases the onset symptoms have been so mild as to escape early medical observation.

Prostration has been marked in some cases and a few men have fainted while awaiting examination at sick call, and many of those performing physical labor have found it impossible to continue.

Within a few hours after onset, the temperature is somewhere between 100 and 104 F.; the pharyngeal mucous membrane is slightly reddened and rather dry; the nose is remarkably clear and unobstructed; the conjunctivae are injected. The patient complains of headache, pain in the back, weakness, pain and tenderness in the eye-balls and sometimes of a burning in the nasopharynx or a slight sore throat. Loss of appetite or even actual distaste for food is observed in about half the cases. The pulse rate is slow in comparison to the temperature and the prostration. Leukocytosis is usually absent in uncomplicated cases, but appears along with the bronchopneumonia. Leukopenia has been observed early in the disease.

In a series of 125 cases examined by Major Richard C. Cabot and his colleagues at Base Hospital 6 between September 28 and October 12, 1918, the frequency of various manifestations were reported by Dr. Cabot as follows: Headache in 87 per cent.; backache and aching in bones in 64 per cent.; foot or toe pain in 18 per cent.; otitis with pain in the ear in 17 per cent.; cough in 92 per cent.; early cough, in the first twenty-four to seventy-two hours, in 80 per cent. Coryza was noticed by half the patients, but Dr. Tobey found a dark red, dry mucous membrane in 90 out of 100 cases of this series examined by him. Sore throat was complained of by 37 per cent., and Dr. Tobey found a dry red pharynx with swollen lymphoid tissue on the lateral wall in 80 per cent. Epistaxis occurred in 35 per cent.; appetite was good in 52 per cent. and vomiting occurred in only 21 per cent. In 100 cases of this series examined by Dr. Hatch, conjunctivitis was not found, but the eyes were injected, perhaps somewhat more than in most fevers. The neck was somewhat stiff in 12 per cent., but this stiffness was never marked. Herpes was observed in 17 per cent. Careful examination failed to reveal any distinctive rash. Among the 125 cases definite signs of bronchopneumonia on admission were present in 40 per cent. The otitis was catarrhal, usually with considerable pain for a few hours, but without enough exudate to bulge the drum. Dr. Cabot expressed the belief that careful examination in a quiet place would reveal consonating râles with diminished breathing and slight dulness in nearly all cases, sufficient evidence for a diagnosis of bronchopneumonia.

This series reported by Major Cabot may be regarded as fairly typical of the disease as it occurred in France about Oct. 1, 1918. The respiratory symptoms were less well marked in the cases seen in

the early months, May, June and July, and in them, cough, otitis media and signs of bronchopneumonia were very uncommonly observed.

Course and Outcome.—In the early months, May, June and July, rest in bed and a purgative were followed by subsidence of the fever and amelioration of all symptoms in twenty-four to seventy two hours, and prompt recovery without further manifestations, except slight weakness and depression. Complications were so rare as to be considered non-existent and the relatively few cases of pneumonia observed were subsequently regarded as instances of mistaken initial diagnosis.

In the later months, from about the beginning of September, the disease has been perhaps less sudden in onset, but the course has been distinctly more malignant and a complicating fatal bronchopneumonia has become alarmingly frequent; so frequent, indeed, as to suggest a new epidemic of an entirely different disease.* Probably this altered character has been due to the colder weather, particularly the cold, wet weather of early fall, the influence of which has been aggravated by the difficulty of troop movements at that time. While some of the cases still followed a course not essentially different from that previously observed, a very considerable proportion, variable in different epidemics, were of the more severe type.

In these more severe cases, distinct evidence of the tracheobronchitis and bronchopneumonia appeared, sometimes within the first forty-eight hours, but usually at about the end of the third or fourth day. In many instances the temperature would fall nearly or quite to normal on the third day, only to rise again along with the gradual appearance of physical signs of extension of the inflammation in the finer bronchi and alveolar tissue of the lungs. This complication was observed particularly in those who failed to go to bed promptly at the onset of the disease and in those who got out of bed before they should, or in those patients who were transported during the febrile period. Pleural effusion occurred in some cases; empyema occurred rarely. Gradual unconsciousness for some hours before death, with considerable extension of the thoracic dulness in the last forty-eight hours, were commonly observed in the fatal cases. When the patient recovered, the fever fell by lysis after six to twelve days.

The death rate in these pneumonias has been high, varying from 5 to 100 per cent. in different epidemics. The death rate for pneumonia of all types, as computed in the office of the Chief Surgeon, A. E. F., represents the ratio between new cases of pneumonia in hospital and deaths from pneumonia in the same period. During July this rate

* The evidence in regard to this suggestion will be discussed subsequently in the section dealing with etiology.

varied from 11.4 to 22.0 per cent. in the different weeks, but for the last week in October it reached 75 per cent.* and continued high during November. The bulk of these deaths resulted from the bronchopneumonia of the influenza epidemic.

In the series of 125 cases studied by Major Richard C. Cabot and his colleagues at Base Hospital 6, there were eighteen deaths, or 14.4 per cent. of the cases of influenza. Inasmuch as 40 per cent. of these cases showed bronchopneumonia on admission, the maximum death rate of the pneumonia cases was eighteen in fifty, or 36.0 per cent. Doubtless many others in the series also developed pneumonia in the hospital so that the death rate for the pneumonia in the series may be placed at 14.4 per cent. as a minimum and 36.0 per cent. as a maximum.

The duration of the febrile period was recorded in 87 of these 125 cases as three days in 11 cases; four days in 7; five days in 10; six days in 17; seven days in 11; eight days in 8; nine days in 11; ten days in 6; eleven days in 3; twelve days in 2; and fifteen days in one case. The relative predominance of three-day and six-day type of fever was considered suggestive of identity with the three-day fever of the spring and summer.

The fever reached a point between 102 and 106 F. at its height in eighty-five of these cases. The pulse rate ranged between 70 and 100, and in 40 per cent. of the cases between 90 and 100. No instances of extremely slow pulse, such as reported elsewhere, were observed in Cabot's series.

Another series of cases reported by Major Thomas K. Martin at Base Hospital 8, Oct. 25, 1918, evidently originated on the transports during voyage from the United States. In this series there were four cases of lobar pneumonia, one of them primary and three secondary to influenza, with one death; 156 cases of bronchopneumonia, of which one was primary, 148 cases secondary to influenza, and seven secondary to bronchitis, with fifty-two deaths. Pleural fluid was found in thirteen cases. It was clear in nine cases, turbid in four cases. Bloody sputum was observed in 118 cases. The fever terminated by lysis between the eighth and tenth day in forty-seven cases; between the tenth and thirteenth day in sixty-one cases. Twenty-two cases of pneumonia developed in the wards, twenty from influenza, one from bronchitis and one in a case of paraplegia. There were 268 cases of influenza at the same time, of which 246 were respiratory; one nervous;

* The rate of 75 per cent. pneumonia case mortality as quoted is probably erroneous owing to (1) the great delay in receiving full reports of total new cases, and (2) to the failure to diagnose and report many of the pneumonias actually developing among the influenza cases.

nine gastro-intestinal; and twelve febrile. Ear complications and sinus involvement were uncommon. Bacteriologic examinations showed the presence of the influenza bacillus and of pneumococci in almost every case. Hemolytic streptococci were not found. The death rate in the pneumonia was 32 per cent.

Designation.—Without regard to the bacteriologic findings or questions of etiology the disease is certainly properly designated as influenza on the basis of its epidemic and clinical characters alone.

PATHOLOGIC ANATOMY

General Considerations.—In the early months of the epidemic the disease was so benign in character that deaths which did occur were invariably ascribed to other cause. Since about Aug. 15, 1918, deaths have become much more frequent and the records of necropsy in this disease have become very numerous. From the clinical evidence it appears that the bulk of the necropsy records are based on complicated cases. The pathology of these later cases will be discussed first.

The Respiratory Organs.—The larynx, trachea and larger bronchi showed swelling, edema, injection and infiltration of the mucous membrane, which was covered by frothy muco-purulent, often blood-stained exudate. The smaller bronchi and bronchioles were also involved in the same process and some of them plugged with mucus.

As a rule, all lobes of both lungs were involved; both lungs were large, dark, heavy and firm. On section, the cut surfaces were very moist, dripping a bloody, frothy fluid; the color was somewhat variegated, often showing a few firmer grayish patches of older consolidation centrally located. Invariably the lower lobes were more severely involved. The whole process in the lungs might be designated as an example of massive, pseudo-lobar form of bronchopneumonia of a very malignant type. Considerable variation in the appearance of the lungs occurred even in the same series. Some prosectors, as for example, Capt. Arthur U. Desjardins, were able to distinguish a type showing more or less fibrinous pneumonia and a type in which this was not present and to foretell from the gross appearance the bacteriologic demonstration of pneumonococci in the former. In some instances gross evidence of hemolysis indicated the presence of hemolytic streptococci which was subsequently confirmed. The following is quoted from a report of necropsy service at Evacuation Hospital 2, A. E. F., by Dr. Desjardins:

"Influenza and its complications: During the recent epidemic about 800 cases were admitted to the hospital from two divisions moving out of a neighboring sector. Of these, twenty-six patients died from pulmonary complications. A remarkable feature of this pneumonia

was its mixed character. In general, the picture was that of a coalescing bronchopneumonia of great virulence, but in several cases it was associated with a certain amount of fibrinous pneumonia. Empyema was present in but two cases. In the development of all these cases at least two organisms were implicated, and in many there were three or even four. It was almost always possible at the necropsy to determine by the appearance of the lungs those cases in which the pneumococcus was present and those in which it was not."

Major George Baehr has enumerated the conditions observed in sixty-seven necropsies performed during the first fifteen days of October, 1918, at the Beau Desert Hospital Center, in a report dated October 21, as follows:

"Necropsies on the individuals dying of influenza pneumonia (Spanish Flu) revealed the following characteristics: (1) Frequency of an associated hemorrhagic tracheo-bronchitis; (2) extensive though irregular involvement of multiple lobes in massive areas of lobular pneumonia consolidation; (3) frequent existence of a much older focus of central pneumonia near the hilus of one or both lower lobes; (4) evidence of an explosive-like spread of the pneumonic process from this central focus to large areas of the adjacent lung parenchyma within the last day or few days before death; (5) relative infrequency of suppuration, empyema thoracis being found only in two cases."

Serous Cavities.—The pleural surfaces were fairly normal or only slightly dulled in luster in many instances; in others, a slight increase in clear fluid with or without a tinge of hemoglobin was noted; in from 5 to 30 per cent., in different series, a large pleural effusion was present, usually serous, but sometimes serofibrinous or purulent; in 10 to 20 per cent. a plastic fibrinous exudate existed on the pleural surfaces. In short, the conditions within the pleural cavities were exceedingly diverse. Pericardial effusion and pericarditis have been observed in a few instances. When large volumes of fluid were found in the chest, the changes in the lungs were less advanced and extensive than usual.

Subcutaneous Emphysema.—This was observed in comparatively few cases in several different outbreaks; beginning in the supraclavicular region or over the anterior chest wall, and becoming more or less generalized over the surface of the body. It appeared to be of no significance as to the outcome of the case. A postmortem study of several such cases by Lieut. David M. Nyquist revealed *B. welchii* in a very few instances but failed to reveal bacteria in the majority of the cases. Mechanical obstruction of small bronchi by plugs of muco-pus

and subsequent solution of continuity in the structure of the lung is the probable explanation of it.

Rectus Abdominalis.—In a very few instances lesions of the rectus muscles have been found. In some cases a necrosis resembling Zenker's necrosis, in other cases hemorrhages into the muscle were present.

Cranial Sinuses.—The first wave of the epidemic in May and June did not have any recognized cases of sinus or aural complications, and as there were few if any deaths from influenza at this time no opportunity presented itself to prove the absence of sinus involvement by necropsy. Clinical evidence of such involvement was entirely lacking. In the later phases of the epidemic, sinus and aural complications were occasionally met with.

Other Organs.—The changes in other organs have been those of acute toxemia, manifested particularly in the kidneys, liver and spleen. Icterus, apparently of hemolytic origin, was observed in a few instances.

Pathology of Particular Cases.—Clinical histories are available in some instances so as to permit a determination of the exact duration of the disease before death occurred. Significant features of a few necropsies on such cases will be presented.

NECROPSY 5002: Patient had a slight cold on Saturday, October 5, but took dinner with friends on that date. He was admitted to American Red Cross Military Hospital 1 from the Hotel Meurice at 6 p. m. on October 7 in a dying condition; died October 8 at 8:30 a. m. Duration of illness was therefore about 60 hours. Pleural cavities contain a few cubic centimeters of cloudy fluid. There are no adhesions. Lungs are both of the size of full inspiration. There is practically no exudate on either pleural surface. The right lung shows the upper two thirds of the upper lobe, the apex of the middle lobe and scattered patches throughout the lower lobe containing solid bluish-red areas, which have ill-defined margins. On section these areas are dark red in color and comparatively airless, the surfaces being bathed with a very large amount of bloody fluid. The remaining portions of the lungs are heavy with congestion and edema, except for a few of the anterior portions, which are dilated and feathery. The outer middle portion of the upper lobe and the outer half of the lower lobe of the left lung are in a similar condition; otherwise it resembles the right. The bronchi of both lungs are deep red in color, bathed with abundant blood-stained frothy mucus and covered with a thin, closely adherent, grayish-yellow, fibrinous pseudomembrane. The peribronchial lymph nodes are not markedly swollen. The sinuses at the base of the skull show some thickening of the mucosa and a small amount of mucoid fluid in the left sphenoid and left frontal. Smears and cultures from the lungs show streptococci and gram-negative bacilli (*B. influenzae*?). Smears from frontal sinus show staphylococci, gram-negative bacilli (*B. influenzae*?) and a short gram-positive bacillus; cultures from the same place show staphylococci. Prosector Major H. E. Robertson.

NECROPSY 3456: Patient was admitted to Evacuation Hospital 2 Oct. 16, 1918, with a diagnosis of acute influenza; temperature, 103 F.; pulse, 116; respiration, 24. October 17, the temperature rose to 104 F.; pulse, 104; respiration, 30.

The temperature remained above 104 F., at times reaching 105 F.; respirations increased to 50, but the pulse rate did not rise above 104 until the day of his death, when it reached 120. Death occurred Oct. 20, 1918, at 11:30 p. m., four days after admission. The pleural cavities each contain about 10 c.c. of clear serum. The parietal pleura is speckled thinly with petechial hemorrhages on both sides, and small tags of fibrin hang from it. The areolar tissues of the anterior mediastinum are moderately infiltrated with glistening, gelatinous material. The posterior and apical portions of the right pleural cavity are obliterated by very firm fibrous adhesions. The apical and posterior surfaces of the right lung are covered with fibrous tags and the pleura is thickened and rough. At the apex of the right upper lobe the pleura is puckered and thickened, and on section the thickened pleura at this point measures 4 mm.; it is whitish in color, very dense and resistant and fibrous in character. Beneath this, the cut surface of the apical portion of the right upper lobe is made up of irregular grayish-yellow areas, all coalescing, and separated here and there by fibrous strands. The middle and lower lobes are large, heavy and dark; their pleural surface has the appearance of pavement, the lines being formed by distended lymph channels. The cut surface is very dark, moist and compact; the lobes are entirely consolidated, but the consolidation is peculiar in that it is made up of coalescing patches of bronchopneumonia massed together. From the atypical appearance one is led to think of a mixed infection. The left lung is in the same condition, except the anterior portion of the upper lobe, the cut surface of which is markedly hyperemic and has, scattered in it, some dark red patches similar in appearance but much larger than the patches ordinarily seen in typical bronchopneumonia. The mucosa of the trachea and bronchi is very hyperemic and bathed in an abundance of thin, frothy fluid. The tracheobronchial lymph nodes are moderately enlarged, unusually moist and slightly bloody. The tissues of the posterior mediastinum are slightly infiltrated with glistening jelly-like material. Prosector, Capt. Arthur U. Desjardins.

NECROPSY 2920: Patient entered Base Hospital 17 Sept. 12, 1918, having been in France one week. He had been sick since landing and had been riding in a baggage car for several days. He died September 12 at 11:50 p. m. The necropsy was performed at 3:25 p. m., September 13. The mediastinum is well covered with fat, the right visceral pleura hemorrhagic and injected and covered with fibrinous deposits. The pericardial cavity contains about 70 c.c. of a straw-colored fluid. The left lung weighs 1 pound 13½ ounces and shows irregular consolidated areas. The right lung weighs 2 pounds 12½ ounces. The left lung floats in water; on section it shows irregular consolidated areas from which frothy mucus exudes. The lobular type is more evident to the sense of touch than of sight. The entire right lung floats in water as do portions from the most nearly consolidated portions. Bronchi are red and inflamed. Cultures from the brain and from the heart blood are negative; cultures from the right lung show *B. influenzae* and *Streptococcus viridans*. Prosector, Capt. Henry W. Cattell.

NECROPSY 3958: Patient entered Base Hospital 8, Oct. 8, 1918, from a newly arrived transport. He died at 4 a. m. October 15. Necropsy was performed at 9:30 a. m., October 15. Pericardial cavity contains about 10 c.c. of a clear yellow fluid. There are numerous hemorrhages on the left side of the pericardium. The right lung is adherent posteriorly and the right pleural cavity contains about 300 c.c. of a cloudy yellow fluid. The lower half of the pleura is covered with a thick layer of yellow fibrinous exudate. The left pleura is slightly adherent at the base posteriorly and is also covered with fibrinous exudate. The right lung has four lobes, the fourth being a very small one at the apex. This is firm and on section is gray and consolidated throughout. The main upper lobe is collapsed and contains some nodules. Its surface is dull, granular and varying in color from light pink to bluish red. Centrally located there is a nodule of gray consolidation the size of a hen's egg. Around the periphery the lung is well aerated and for the most part of a light pink color.

The cut bronchi exude thick yellow pus. The middle lobe is well aerated, light pink in color and shows a few hemorrhagic areas. Pus exudes from the cut bronchi in this lobe also. The lower lobe is a gray consolidated mass of friable tissue and on pressure exudes thick pus. In the left lung the upper, middle and anterior portions of the lower lobe are aerated. Surfaces of the upper and middle lobes are of a dark red color; on palpation small nodules are felt throughout. The posterior half of the lower lobe is consolidated and nodules may be felt. The larger nodules in the upper lobe are gray and exude pus everywhere when squeezed. For the most part, the tissue is spongy, light pink to deep red and quite friable. At the periphery and at the base there is a dark red consolidation from which a considerable amount of pus exudes. Bacteriology: *B. influenzae*, pneumococcus and a gram-positive bacillus. Professor, Lieut. William L. Aycock.

Variation Depending Upon Chronicity.—These four abbreviated protocols are fairly typical examples of the records of many hundreds of cases coming to necropsy in September, October and November, 1918, and indicate the diversity of picture observed within the thorax. These differences appear to have depended essentially on the rapidity with which the patient succumbed. The fulminant cases showed a picture of malignant coalescing bronchopneumonia which rapidly involved almost all the pulmonary tissue. The more chronic cases showed distinct foci of older gray consolidation; usually multiple with recent more extensive, even general, spread of the pneumonic process. Particular attention is directed to the presence of these nodules of older inflammation because they assume importance in the subsequent discussion of the epidemiology of the disease.

BACTERIOLOGY

Clinical.—The bacteriologic examinations made during life on sputum or material from the pharynx have shown various organisms, usually mixed together. The interest in many instances has centered on the question of Pfeiffer's bacillus and reports in regard to it have shown the very widest variations. Cultures made on blood-agar or on hemoglobin-agar have revealed, in the large majority of cases, pneumococci, streptococci, influenza bacilli, staphylococci and gram-negative cocci. Blood cultures taken during life have usually been negative, but in a moderate proportion of the cases have shown pneumococci or streptococci. Fluids obtained by puncture from the pleural cavity or from the lung tissue have shown the same organisms and at times the influenza bacillus. In certain localities, notably in Base Section 2 (Bordeaux and vicinity) and at Camp Coetquidan, enormous numbers of gram-negative cocci, identified as meningococci, have been found in the sputum during life and in the lungs at necropsy in a certain number of cases. It is probable that these were instances of the pulmonary form of cerebrospinal fever, either primarily such or possibly complicating influenza. Attempts to detect a filterable virus

have been reported, but experiments of this kind have not been carried out in the American Expeditionary Forces.

At Necropsy.—At necropsy, also, the bacteriologic findings have been variable and have usually shown a mixture of various species of microbes. Influenza bacilli, pneumococci of various types, hemolytic and non-hemolytic streptococci have occurred most frequently in the infiltrated lungs. Postmortem blood cultures have shown *B. influenzae* in a few instances, pneumococci and streptococci in a considerable number of cases. Cultures taken from the cut surface of the lung at necropsy in the series of necropsies at Base Hospital 17, made by the staff of the Central Medical Department Laboratory during September, 1918, showed influenza bacilli in 40 per cent. of the cases, hemolytic streptococci in 30 per cent. and pneumococci in 40 per cent., Group IV, Type I, Type II and Type III in order of frequency. In many cases, two or more of these organisms were isolated from the same tissue. More significant, perhaps, have been those necropsies in which a more thorough bacteriologic survey of the respiratory tree has been carried out by culturing in turn the mucous membranes of the trachea, large and small bronchi and alveolar tissue, such as have been reported by Capt. Richard M. Taylor and his co-workers in Base Section 1 (St. Nazaire and vicinity). In fulminant cases, large numbers of influenza bacilli were found, especially in the trachea and bronchi, sometimes apparently in pure culture. In most instances, however, the mucous membrane of the respiratory tract showed a mixture of organisms; in the trachea, influenza bacilli, streptococci, staphylococci, pneumococci, gram-negative cocci and occasionally larger gram-negative bacilli; farther down, influenza bacilli, pneumococci and streptococci; still lower, influenza bacilli, and one species of the cocci, and finally in the consolidated alveolar tissue, the pneumococcus or the streptococcus alone, as a rule, but sometimes mixed together or even associated with the influenza bacillus in this tissue. These findings suggest that the disease has been essentially due to an invasion of the respiratory tract by influenza bacilli, followed by and associated with other pharyngeal organisms, and that the fatal outcome, in most instances, has been brought about particularly by these secondary invaders, in some instances streptococci, in others pneumococci.

The reports from some hospitals indicate that the important secondary infections were due to pneumococci, but in those instances in which type determination was carried out, the strains usually fell into three or four type groups, a considerable proportion of them belonging to Group IV of the classification of the Rockefeller Institute. In other hospitals streptococci were found to be the important secondary invaders. The explanation of these results is not entirely clear. It is

possible that the distinction between pneumococcus and streptococcus has not always been accurately made, and that there has been a tendency in one place to call all these organisms pneumococci and in another to call them streptococci. These reports suggest, however, that the secondary invaders may also have spread from patient to patient, possibly within the hospital wards. In certain series of necropsies, where considerable attention seems to have been devoted to the identification of the cocci in the lungs, these invaders were found to be quite variable, even in bodies coming from the same hospital ward, indicating that their specific nature depended on the type of organisms which happened to be present in the upper respiratory tract of the man at the time of his illness, rather than on contagion.

ETIOLOGY

Infectious Nature.—The epidemic occurrence of the disease leaves no reason to doubt its infectious nature. As in all infectious diseases, contagion and susceptibility require consideration in the etiology.

Susceptibility.—The military population affords little contrast in respect to age and sex. However, it is certain that female nurses have been attacked by the disease with some deaths. In the series reported by Major Richard C. Cabot, there were sixty-three cases of influenza in the personnel of the Base Hospital 6, itself. Of these, forty-three were enlisted men, five were officers, and fifteen were nurses, representing 12 per cent. of the enlisted personnel, 10 per cent. of the officers and 15 per cent. of the nurses. The disease was distinctly milder in the nurses and officers than in the enlisted men. The relative care possibly explains this difference. Older men, particularly those beyond the age of 50, appear to have escaped to such an extent as to suggest a real immunity. Men of this age in the A. E. F. have been relatively few in number and have probably enjoyed better living conditions than most of the younger men, so that the evidence of their immunity should not be too readily accepted as conclusive. Young children of the civilian population appear to have suffered to a considerable extent, although accurate information has not been obtained. Of the soldiers a very large proportion has been found susceptible. In some companies as many as 90 per cent. have been stricken within a period of ten days, and occasionally from 30 to 50 per cent. of a company have reported sick within a period of two days. High incidence of the disease has been observed in organizations performing exhausting duties and in those exposed to cold and wet, and without proper nourishment, particularly in units arriving on crowded transports, making long journeys in troop trains and in those undergoing severe training. Fatigue evidently plays a part in increasing susceptibility,

and the influence of exposure to cold and wet is clearly indicated. During the summer the outbreaks seemed to be related to dust in the atmosphere, the disease becoming epidemic after a long, dusty march, or after a few days of dry, windy weather in camp. Inadequate ventilation has played an important part, probably by decreasing resistance as well as increasing exposure to contagion.

Contagion.—The malady is unquestionably highly contagious. Some of the epidemics have been explosive in character, suggesting that the virus had become generally distributed throughout the organization, and that the exact moment of onset of the disease had been subsequently determined by some general factor influencing susceptibility, such as a hard day's work, a dusty day or a cold, wet night. It is possible that general distribution of the virus at mess by infected food or utensils, infected by some member of the kitchen force, may have caused some of these explosive outbreaks. Members of the Medical Department attending cases of the disease have very frequently contracted it, and in many organizations the epidemic has progressed gradually, involving relatively few new victims each day, after the manner of a disease spread by contact. The virus undoubtedly exists in the secretions of the upper respiratory tract, from which region its dissemination by coughing, sneezing and talking, as well as by contact of hands or various utensils, readily occurs.

Relationship of the Summer and Fall Epidemics.—The identity of the summer epidemic with the disease prevailing after September 1 may be called into question, particularly because of the benign character of the earlier outbreaks and the high death rate observed later. In the later months bronchitis and bronchopneumonia have been very common, while such involvement was extremely rare in the summer. In favor of the essential identity may be mentioned the similar epidemic character of the outbreaks, the clinical resemblance between the milder autumn cases and those of the summer, the rather clear evidence indicating a gradual increase in malignancy as the weather has become colder, and the similar bacteriologic findings during life. Most convincing, perhaps, is the similar epidemic character, which alone almost suffices to prove the essential unity of causation for the disease in the two seasons. Those medical officers who have observed the disease in both seasons are inclined to the view that the primary disease is essentially the same, with the secondary complication of bronchopneumonia in the colder weather. The unfavorable influence of cold and exposure is universally recognized in relation to this disease.

Specific Organism.—In its epidemiologic, clinical, bacteriologic and pathologic features, the disease is everywhere recognized as being

identical with influenza as it was observed in the pandemic of 1889-90. The bacterial findings are those of influenza. In the A. E. F. the bacillus of Pfeiffer has been demonstrated in a very large percentage of the cases properly examined; in several series it has been demonstrated in every case. The other bacteria isolated, namely, streptococci, pneumococci, gram-negative cocci, although undoubtedly the cause of death in many cases, can be excluded from consideration as the primary cause of the epidemic disease, because of the inconstancy with which any one specific type has been encountered. The possible causative relation of the bacillus of Pfeiffer cannot be similarly excluded. On the other hand, the causative relation of this organism cannot be accepted as proven. During this epidemic, as during previous epidemics of influenza, a considerable proportion of throats of persons not suffering from the disease have been found to harbor this organism or organisms indistinguishable from it by the methods employed.

A report by Major Kenneth Taylor under date of Nov. 5, 1918, of work done in the Base Laboratory, District of Paris, presents evidence on this question. In a series of thirty-five selected cases of epidemic influenza without signs of bronchopneumonia, cultures of swabs from the nasopharynx showed streptococcus in 57 per cent., pneumococcus in 74 per cent., and influenza bacillus in 46 per cent. In a second group of fifteen cases diagnosed clinically as bronchopneumonia, cultures of the sputum revealed hemolytic streptococcus in 33 per cent., pneumococcus in 87 per cent. and influenza bacillus in 87 per cent. Only one of these patients died and in his case pneumococcus and hemolytic streptococcus were present in the lung at necropsy. In four cases the sputum was inoculated into mice and pneumococcus of Group IV and the influenza bacillus were recovered from the animal's peritoneum and heart blood. In a third group of twenty-two meningitis contacts, nasopharyngeal cultures showed influenza bacilli in 48 per cent.

A report under date of Sept. 5, 1918, by Capt. Alan M. Chesney and Lieut. Marcus P. Neal, on the epidemic of influenza at the Val-dahon Camp, contains the records of nasopharyngeal cultures from 106 cases of influenza, of which 46.2 per cent. showed the influenza bacillus and 20.7 per cent. showed streptococci. In a series of twelve normal individuals, direct contacts of these cases, the influenza bacillus was found in 41.6 per cent. and the streptococcus in 25.0 per cent. A series of forty-two normal individuals, not contacts, examined in the same way, showed influenza bacillus in 7.0 per cent., and streptococcus in 10.0 per cent.

In order to settle in a convincing fashion the relation of the bacillus of Pfeiffer to the disease it would be necessary to carry out a series

of very carefully controlled experiments on a group of thoroughly segregated men, preferably those confined in a prison which has entirely escaped the epidemic. It will not be sufficient to produce by the inoculation of pure cultures the clinical manifestations of influenza merely in the individual inoculated, but a critical demonstration should include the reproduction of the disease with its characteristic epidemic feature.

A limited number of experiments have been reported by various investigators suggesting that the causative organism may be a filterable virus. More detailed reports of experiments on a considerably larger scale will be required before the results can be accepted as conclusive. In addition to the numerous sources of error which require attention in all investigations of filterable viruses, there is here the special confusing element of the filterable virus of common colds,* a virus which appears to be capable of causing the signs and symptoms of influenza in the individual inoculated, but has not been proved to be connected with the genuine pandemic disease.

Until conclusive experiments have been carried out to decide the claims of the bacillus of Pfeiffer and of the filterable virus as the cause of influenza, one should keep an open mind in regard to the matter. It appears fruitless to attempt to settle the question by debate.

TREATMENT

Isolation.—Influenza patients should be segregated in a separate ward and the strictest precautions taken to prevent the spread of the disease to other patients in the hospital and to the hospital personnel. In addition, because of the serious nature of the secondary infections, individual isolation within the ward by means of cubicles, masks, thorough sterilization of every article after use in contact with each patient, individual personal equipment for each patient as far as possible and extraordinary cleanliness of person and clothing on the part of attendants and nurses are required. Gross defects in the program of isolation will usually be found unless the medical officer in charge has given close personal attention to the minute details. Elaborate material equipment and extravagant use of linen will not effectively compensate for lack of intelligence, skill and diligence in the personnel.

Therapeutics.—For the treatment of the individual patient, the most important and essential feature is to put him to bed promptly and keep him there until his temperature has become normal and his appetite has returned. The bowels should be opened at the outset. Abundant ventilation and adequate provision to keep the patient warm

* Foster, George B.: The Etiology of Common Colds. *J. Infect. Dis.* **21**: 451, 1917. This paper cites other literature on the subject.

are essentials. In this way the danger of bronchopneumonia and death are reduced to a minimum and the attack remains benign in character and short in duration. Promptness in the institution of these measures is of greater importance even than the most skillful subsequent medical treatment and the most careful nursing.

Complicating bronchopneumonia sometimes appears early, but, as a rule, only after the second day of the illness and in neglected cases, particularly in patients who have failed to report sick, have refused to go to bed or have been transported a considerable distance to a hospital after the onset of the influenza. For the bronchopneumonia, careful nursing and feeding are the chief elements in successful treatment. The patient should be encouraged to take plenty of food, especially milk, eggs and broth, and abundant fluid. Tepid sponging and attention to the comfort of the patient in little things are indicated, if the nursing personnel is sufficient to permit it. Various drugs have been employed, such as quinin to the physiologic limit, whisky, three ounces every four hours, tincture of digitalis in full doses. Opinion as to the value of these drugs varies considerably, and the death rates in those series, in which they have been employed, do not furnish convincing argument in their favor. One series of cases treated systematically with full doses of atropin showed a very high death rate. Pleural effusion should not be allowed to pass unnoticed.

Under field conditions the treatment has often been hampered because the medical officers, nurses and enlisted men of the Medical Department, already inadequate to care for the excessive numbers of patients, have had their own ranks decimated by the disease.

At least two weeks should be allowed for convalescence before returning to duty.

PREVENTIVE MEASURES

Hygienic measures have to be directed to prevent or diminish contact with the virus of the disease, to increase and retain at a high level the natural resistance to the infection and also to avoid the serious complications in those who have become ill.

Avoidance of Contagion.—For troops located in country districts quite apart from the civil population, a thorough segregation may prevent the entrance of the infection. This would entail the denial of all leave and the strict avoidance of contact and association with outsiders. Too much reliance should not be placed on the effectiveness of such measures, and during the time of a pandemic the advent of the disease should be expected and the measures to meet it prepared in advance. In many organizations the introduction of the disease will prove inevitable.

To diminish the danger of spread within the organization, increased floor space for sleeping quarters, cleanliness of quarters, thorough ventilation night and day, avoidance of all dust, separation of heads of adjacent sleepers in bunks by board, paper or shelter-half partitions between bunks, effective prohibition of spitting and of open coughing and sneezing, immediate segregation of all men with coughs and colds, sterilization of mess kits by boiling water after each meal; strict care in regard to individual use of personal equipment, such as pipes and towels; daily sunning of bedding and clothing, and thorough drying of clothes and shoes should be provided for.

As soon as cases of the disease are recognized the patients should be provided with face masks and be segregated promptly, preferably in a hospital. Early recognition of these cases is so important that it is well for the medical officer to examine his entire organization every afternoon, sending to the hospital every man with a temperature above 99.5 F. Early recognition makes possible early treatment and also the removal of a source of infection from the organization. If wounded and sick are transported together, all patients should be masked in transit.

Increased Resistance.—There can be no doubt that depressing influences play an important part in determining the moment of onset of influenza and the severity of the attack. Overwork, overcrowding, exposure to cold and wet, breathing a dusty atmosphere, bodily discomfort, as well as loss of sleep and alcoholism, may be mentioned as important depressing influences. In office workers, the lack of sufficient exercise has evidently contributed to susceptibility. Resistance may be kept up to normal by avoiding these depressing influences, and may probably be increased considerably by proper daily calisthenic exercise and moderation in hours of labor. Many organizations in the A. E. F. have been attacked by the disease without it ever becoming sufficiently epidemic to disturb seriously their work, and have escaped without a single death. Others have been paralyzed by the epidemic, and in some the number of deaths has been considerable. The hygienic factors mentioned above seem to have played a decisive part in determining these differences.

Acquired Immunity.—There is very little reliable information bearing directly on the question of acquired immunity. The experience of Base Hospital 6 at Bordeaux, reported by Major Richard C. Cabot, is the most interesting. At that hospital, eighteen of the personnel had influenza (three day fever) during June and July, 1918. Between September 28 and October 12, there occurred sixty-three cases of influenza in the same hospital personnel, and not one of these sixty-three persons belonged to the group of eighteen who had had the

disease earlier. This observation suggests an immunity lasting more than two months. On the other hand, there is the personal experience of several officers who have devoted special attention to the study of this disease, who have themselves suffered two, three and even four attacks within a period of six months. On account of the uncertainty in regard to diagnosis, this evidence cannot be accepted as scientifically reliable.

The relatively few cases of the disease among the older men has been regarded as evidence of an immunity persisting since the epidemic of 1889. However, it has been possible to find a few very definite instances of persons who suffered from the disease in 1890 and again in 1918. On the whole, the evidence of a lasting immunity is not very convincing. Its critical investigation is a matter for the future.

Bacterial vaccines for the artificial immunization have not been generally employed in the A. E. F. They have been used to some extent in the United States. The latest available information indicates that their use is considered to be in the experimental stage.

EPIDEMIOLOGY

General Considerations.—The origin of the great pandemic of influenza of 1918 is involved in considerable obscurity, and it may never be possible to elucidate the question in a convincing manner. It seems certain that the epidemic outbreaks first appeared in Europe, apparently either in France, Italy or Spain, and that the disease subsequently spread northward to Belgium and England and across the sea in ships to America and Africa. It is known that the disease also prevailed in Germany and Austria during the summer and fall, and special meetings of the medical societies of Berlin and of Munich were devoted to it in July, 1918. In August and September the disease was carried across the sea to America and to South Africa, where it has spread extensively. The conditions for its incubation probably bear a relation to the great war and the altered living conditions dependent on it, but the relation is far from clear. Theoretical considerations must enter largely into the discussion of its origin because of the incompleteness of accurately recorded observations.

In searching for the origin of any pandemic disease it is necessary to recognize that such a disease does not arise entirely anew, each time; especially is this evident for a disease which has previously existed in pandemic form. It must have existed in one or more, probably in many localities, as an endemic disease for a long time. In general, epidemic diseases, such as bubonic plague, cholera and yellow fever, are known to have existed for long periods in certain endemic foci, from which they have suddenly spread and assumed epidemic or even

pandemic character. Again, after the subsidence of the general pandemic, the disease has often remained established in certain new localities, potential new endemic foci, from which it has gradually disappeared or subsequently remained endemic, or even again spread as an epidemic. In tracing the origin of an epidemic disease, therefore, it is required first to ascertain its endemic focus or foci and then to recognize the particular places where the endemic disease has first spread to such an unusual extent as to merit recognition as an epidemic disease, and third, to trace the subsequent extension. In the case of a pandemic this is often impossible, and one can only discover the port at which the disease was introduced from abroad and trace its spread from that point..

Epidemic in A. E. F.—The earliest reported outbreak of epidemic proportions in the A. E. F. was that which appeared about April 15, 1918, at Rest Camp 4 in Base Section 2, near Bordeaux, reached its height on April 22 and ceased on May 5. The Base Epidemiologist, Lieut. J. LaBruce Ward, in a report dated May 8, 1918, stated that the disease occurred simultaneously in camps widely separated with no communication between the men; whether the French civilians were similarly affected was not ascertained; clinically, the disease resembled influenza except for its short duration and absence of complications. In a later communication, under date of May 20, 1918, he says, "The symptoms were those of influenza. The patient was afebrile on the third or fourth day and able to work within a few days thereafter. There were no signs or symptoms of pulmonary involvement except a mild bronchitis in about 10 per cent. of the cases." Several hundred cases were observed; in one camp with a strength of 3,400 men, there occurred eighty cases in two days; in another camp of only 180 men, twenty cases occurred in one day. Both white and colored troops were attacked.

May 26, 1918, Capt. Clifford B. Farr reported an outbreak of influenza at the Quartier de Beaumont, Tours, beginning on May 1, 1918, and ending May 24, 1918, with a total of 117 cases. In a few patients there were present marked laryngitis, bronchitis, occasionally localized at one or the other base. Herpes was observed in a few cases. The height of the epidemic was reached on May 14, on which day there were eighteen new cases.

May 3, 1918, a sharp outbreak of the disease appeared in the personnel of Camp Hospital 23 at Langres, with twelve cases on the first day, ten among the enlisted men and two among the French civilian employees. This has been reported by Lieut. Alan C. Sutton. In all there were forty-four cases. The symptoms were severe headaches, usually occipital; severe backache and general muscular pains, a gen-

eral soreness in the chest, especially substernal, with moderate cough and a mild sore throat. Onset was abrupt with rapid rise in temperature to 103 F., but no distinct chill. Extreme prostration was characteristic of the disease. Some of the men fainted while on duty and had to be carried to bed. Recovery was rapid in practically every case, the average stay in hospital being two days. There were no complications.

May 22, 1918, Major A. S. Bowen, Commanding Officer of Base Hospital 101, St. Nazaire, reported a mild epidemic of influenza in the personnel of that hospital, beginning May 11 and ending May 19. In all, fifty-four patients were treated in the hospital. The cases arose in small nests of contacts working together. Only six cases developed among patients in the hospital. The cases were practically all of a mild respiratory type, and showed a high percentage of cultures of influenza bacillus.

May 11, 1918, a memorandum was issued by the French Service de Santé-Militaire to all its directors in France, calling for telegraphic reports of all outbreaks of grippe and describing the characters recently observed as follows: "Evolution breve ou benigne mais extension rapide et massive des groupes atteints." This is proof that reports of outbreaks of some importance had already reached the French authorities before May 11.

An outbreak which served to bring the disease into greater prominence in the A. E. F. occurred in the garrison at General Headquarters, Chaumont, from May 13 to May 24, twelve days, during which period 132 cases of the disease were recognized. In the Company of the Fifth Marines, which served as Headquarters Guard and as Municipal Police of Chaumont, fifty-four men were sick in a total strength of 172 men. In this Company, nineteen men fell sick on May 15, and twenty-two more on May 16, sufficient to interfere most seriously with the military duties required of this organization. The attending surgeon, Major Henry Beeuwkes, recognized the existence of an epidemic of respiratory infection, reported it to the Chief Surgeon and to the Director of Laboratories and Infectious Diseases, and asked for assistance to control it. This outbreak necessarily received wide attention in the A. E. F. and at once brought to light information in regard to other similar outbreaks. At Chaumont itself, the medical officers of Base Hospital 15 described a similar small epidemic, which ran through one entire ward of that hospital early in April, 1918. The French physicians practicing among the civilian population were perfectly familiar with the disease, designated it as grippe and stated that it had been extensively prevalent in the civilian population of Chaumont from March 15 to May 15, 1918.

At Bourbonne-les-Bains a sharp outbreak occurred among the officers of the Third U. S. Cavalry in the period May 20 to 24.

In Base Section 2, Bordeaux, the hospital personnel developed fourteen cases between May 15 and May 30. At Camp Hospital 66, St. Sulpice, near Bordeaux, an increase in undiagnosed fevers was noticed in the week ending May 13, and in the following week a distinct epidemic of 100 cases was recognized. In June and July the disease appeared in many localities in this Base Section.

By June 1, 1918, the disease had become very widespread in all sections of the A. E. F. in France and in the French and British armies as well, and apparently also in the German and Austrian armies.

The evidence fails to indicate any definite single point at which the new disease penetrated the border of France as an epidemic. It suggests rather that outbreaks occurred at several separate places in April and May, and that the disease became practically generalized in June. There is also a distinct suggestion that the civilian population was afflicted with the disease in March and April before the military outbreaks were recognized.

Outbreaks in Italy and Spain.—A note in the report of the Commission Sanitaire des Pays Alliés, for April, May and June, indicates that the disease became epidemic in the Italian navy in the first two weeks of May. Alberto Lutraria, the health commissioner of Italy, states that the disease was brought from America, but the observations on which this statement rests are not known, although it is not improbable that some association with Americans has been traced by the author. The suggestion that the epidemic was introduced from America is supported by the fact that it appeared at a time when large numbers of Americans were arriving in Europe, which is indeed an outstanding feature correlated in time with the onset of the epidemic. This view was evidently shared by some of the medical officers who arrived in France from the United States in the latter part of 1918. However, this conception is distinctly opposed and probably completely disproved by the fact that the epidemic was subsequently introduced into America in August and September and found there a most fertile soil for its spread.

In Spain the disease appeared in epidemic form about the middle of May and this outbreak received great publicity, sufficient to lead to the popular appellation of Spanish influenza. The very rapid and extensive spread of the disease in Spain would indicate that it had been introduced from without rather than transformed from the endemic state in that country. This also appears to accord with the view of those who have studied the epidemic in Spain.

Endemicity in France.—A possible explanation of the origin of the

epidemic may be found by regarding the incoming Americans as new fuel furnished to a smoldering fire already existing in Europe. In other words, influenza may be regarded as endemic in France, but relatively mild in character, until the large number of susceptible Americans, unused to campaign, unaccustomed to the climate, the houses, customs and work demanded of them, were suddenly brought into contact with it. In particular, Americans have been accustomed to more adequate provision for heating their houses and for drying their clothing than have been available for them in France. In the winter of 1917-1918 the living conditions in the cantonment camps in the United States apparently presented difficulties in regard to heating and overcrowding similar to those in France, but there the disease observed was evidently essentially different from the influenza of 1918. On the other hand, the American troops in France in 1917 began to show, as early as October, 1917, a very considerable rise in the influenza morbidity. The data available in the office of the Chief Surgeon, A. E. F., show an influenza morbidity per 100,000 of 321 in July, 438 in August and 404 in September, rising to 1,050 in October, 1,980 in November and 2,480 in December, 1917, in which month the total number of new cases of influenza reported was 3,520. That a considerable proportion of these cases were actual infections with the bacillus of Pfeiffer is proven by the necropsy findings in fatal cases of bronchitis and bronchopneumonia, especially those performed by Major H. E. Robertson at Army Laboratory 1, Neufchateau, in November and December, 1917, and January, 1918. In these cases the bacillus of Pfeiffer was found in the scattered patches of lung involved in the bronchopneumonia and also with great frequency in the cranial sinuses. These necropsy findings were, at the time, recognized as essentially new for young adult Americans, and, in a discussion at Army Laboratory 1 during December, 1917, they were considered as being of possible important significance for the future morbidity of American soldiers in France. In the British Army in France there is definite evidence of epidemics showing the same pathologic condition, during the winter of 1916-17,² and at Aldershot³ in September, 1917. There can be little, if any, doubt that this disease was essentially the same as that which attacked the American soldiers late in 1917.

The essential similarity in the anatomic changes observed in the later epidemic and in these earlier cases warrants the quotation of the important parts of a few of these early protocols.

2. Hammond, J. A. B.; Rolland, W., and Shore, P. H. G.: Purulent Bronchitis, *Lancet* 2:41, 1917.

3. Hallows, F. N.; Eyre, J. W. H., and French, H.: Purulent Bronchitis: Its Influenzal and Pneumococcal Bacteriology, *Lancet* 2:377, 1917.

NECROPSY 2. The patient enlisted August 12, 1917. He has had a cold for the past few weeks but was not admitted to Camp Hospital 4, Neufchateau, until Oct. 24, 1917, with symptoms of prostration, dyspnea, fever, cough and marked evidence of general sepsis. Pneumococcus (Group IV) was isolated from the sputum by mouse inoculation. The man died October 26 at 11:55 p. m. At the necropsy the left lung was found expanded to full inspiration; the surfaces were smooth; at the inner anterior margin of the upper lobe were several firm areas, the largest about the size of a walnut, grayish to bluish in color, with distinct puckering of the surrounding pleural surfaces. A few similar areas were located at the outer posterior margin of the lower lobe. Scattered throughout the pulp were smaller foci of increased consistence. Remaining portions of the lung were light, feathery, particularly the lingula. On section the firm areas had moist grayish surfaces and were comparatively airless. From the cut bronchioles purulent fluid escaped on pressure. The bronchial mucosa was bathed by a mucopurulent frothy liquid and was distinctly reddened and swollen. Peribronchial lymph nodes were markedly swollen, soft and red. There was no evidence of tuberculosis. The larynx and trachea showed the mucosa congested, especially near the bifurcation of the trachea, and covered by a frothy, mucopurulent exudate; the lymph nodes at the bifurcation were very greatly swollen, reddened and friable. The middle ears and mastoids were normal; the sphenoidal air cells were full of thick, yellow fluid and the mucosa was swollen and congested. The posterior ethmoidal cells contained some thin yellowish fluid, while the anterior cells were apparently free; the mucosa in both groups was distinctly thickened. Bacteriologic examination showed *B. influenzae* and grain-positive diplococci in sphenoidal sinus, in the lungs and in the liver. Prosector Major H. E. Robertson.

No less than six of the first nine necropsies recorded at Army Laboratory 1 were essentially identical with this one, and a large proportion of those performed in the training area during November, December, 1917, and January, 1918, were similar.

NECROPSY 87: The patient was admitted to Base Hospital 66, Neufchateau, February 7, 1918, complaining of severe cold, with cough, which began three days before; also pains in his joints and sore throat. February 13 a fine papular eruption appeared, especially over the chest and abdomen. At this time his temperature was 102 F., pulse and respiration rapid. Harsh râles were heard at the base of the right lung and fine moist râles in the lower lobe of the left lung. Death occurred February 13, 1918, 11:35 p. m. Necropsy, February 14 at 9:30 a. m.: The pleural cavities were free from abnormal fluid; the left visceral and parietal pleura were bound together by fresh fibrinous adhesions, uniformly distributed over the lower lobe. The right pleural cavity presented numerous firm fibrous adhesions over the surface of the middle and lower lobes, especially at the base. The left lung was rather voluminous; the upper lobe was grayish in color and air-containing; the lower lobe was of darker hue, mottled with reddish purple. The pleura here and there was covered with a yellowish shaggy friable exudate. Beneath these areas and also scattered in the deeper areas of the lung tissue were rather firm airless areas. The bronchial mucous membrane was intensely swollen and covered with mucopurulent secretion; this condition was likewise seen in the bronchioles. The pulmonary vessels showed no thrombi; the bronchial lymph nodes were swollen and friable. On section there were found, scattered throughout the lower lobe, corresponding for the most part with the bronchioles, areas varying in size from a pea to a walnut. In color they varied from gray to purple; were firm and quite friable. The lung tissue in the immediate neighborhood showed intense congestion. In the right lung, the upper lobe was grayish in color and air-containing; the middle and lower lobes were voluminous, dark red in color. The pleura was rough and showed numerous fibrous

tags. In all other respects it resembled the left lung. The tracheal mucosa was intensely swollen and covered with an abundant mucopurulent exudate. The middle ears were normal; the mucosa of the posterior and anterior ethmoids was slightly swollen and moist; no purulent exudate was present; the frontal sinuses were normal. Bacteriologic examination of the ethmoidal sinuses by both smear and culture was negative. Prosector, Lieutenant Hugh R. Spencer.

NECROPSY 139: The patient was admitted to Base Hospital 66, Neufchateau, March 13, 1918, having had a cough since March 6. On admission, he had severe headache, shortness of breath, pain in the right side, with temperature of 102.4 F., pulse 120, dulness over both lower lobes and moist râles everywhere. Pneumococcus, Type II, was isolated from the sputum. Death occurred March 20, 1918, at 3 a. m. Necropsy at 9 a. m. same date: Pleural surfaces were everywhere smooth and there was no abnormal fluid. In the lower lobes of both lungs, there were numerous small, grayish, consolidated areas, corresponding with the terminal bronchioles, which were considerably swollen. The lung tissue elsewhere was intensely congested and of a deep red color. The lymph nodes at the bifurcation were swollen, soft and red. Culture from the heart was sterile; cultures from the lung showed pneumococci and influenza bacilli. Prosector, Major F. H. Foucar.

NECROPSY 194: The patient was admitted to Camp Hospital 15, Camp Coetquidan, April 5, 1918, with a diagnosis of measles. April 8, he developed signs of diffuse bronchitis, with marked dyspnea and cyanosis; the white blood cells numbered 8,400; the sputum showed chiefly *B. influenzae*. Death occurred April 13, 1918, at 1:30 p. m. Necropsy April 13, at 4 p. m.: The pleural cavities were free, without exudate or adhesions; the fluid was not increased. The right lung weighed 660 grams. Externally all three lobes were irregularly mottled, with raised, grayish margins and depressed dark brownish centers. On section the same characteristic mottling was seen throughout all lobes. Interspersed between the grayish aerated tissue, from which a bloody froth exuded, were dark red firm areas of consolidation, the latter being found especially near the hilum. The bronchi were filled with a greenish purulent material. The left lung weighed 630 grams, and was identical in appearance with the right. Bacteriologic examination of pus from the right and left bronchi showed pure culture of *B. influenzae*. Prosector, Lieutenant Edward H. Mason.

The records of these necropsies, especially those from Neufchateau, the laboratory center of the advanced training area in 1917, indicate very clearly the prevalence of influenzal bronchopneumonia from October, 1917. The almost epidemic character of the disease is indicated by the data presented in Table 1. The influenza rates per 100,000 of 1,050 in October, 1,980 in November and 2,480 in December, 1917, really indicate a greater relative prevalence of influenza at that time in the A. E. F. than occurred in the fall of 1918, when the respective influenza morbidity rates were 826 in September, 2,176 in October and 1,356 in November. The total number of American troops in France was relatively small during that winter—141,995 effective mean strength in December—so that the prevalence of influenza did not lead to the recognition of an actual epidemic. Furthermore, the overcrowding in quarters, which seems to have had a definite relation to many of the later explosive outbreaks, had not become such a distinct feature at that time. In addition, the cold, wet weather,

exposure and unusual living conditions furnished explanations for the morbidity which were no longer adequate during the hot weather of May and June, 1918. Until May, 1918, therefore, the prevalence was that of an endemic disease, with perhaps an occasional outbreak suggesting epidemic character.

TABLE 1.—DATA IN REGARD TO INFLUENZA AND PNEUMONIA, ESTIMATED FROM RECORDS IN THE OFFICE OF THE CHIEF SURGEON, A. E. F. BY MONTHS

	Mean Strength A. E. F.	Influ- enza Cases	Influ- enza, Rate per 100,000	Pneu- monia Cases	Pneu- monia, Rate per 100,000	Pneumonia Deaths	
						Number	Case Ratio
1917:							
June.....	14,361	5	35
July.....	15,555	50	321	18	116
August.....	26,703	117	438	15	56
September.....	44,744	180	403	28	63
October.....	70,079	735	1,050	98	140
November.....	106,990	2,120	1,980	192	178
December.....	141,995	3,520	2,480	508	358
1918:							
January.....	188,652	3,660	1,940	980	520
February.....	229,316	2,195	958	480	210
March.....	286,521	2,420	844	625	218
April.....	437,003	1,850*	423*	252*	58*
May.....	503,265	456*	73*
June.....	739,042	4,520	748	660	89
July.....	988,015	3,983	403	478	48	64	13.4
August.....	1,275,595	6,393	501	792	62	142	17.9
September.....	1,545,812	12,769	826	1,683	109	422	25.1
October.....	1,741,593	37,904	2,176	5,353	307	3,129	58.5
November.....	1,805,343	25,287	1,356	4,077	219	1,935	47.5

* These figures are regarded as quite inaccurate because of incomplete tabulation.

Origin of the Epidemic.—From the preceding discussion it is evident that the possibility that the epidemic actually originated in France has to be considered. The alternative possibility is that the disease first became epidemic elsewhere and was introduced into France in the epidemic form in the spring of 1918. The problem is made more complex because of lack of absolute certainty in regard to the nature of the disease and the identity of the epidemic disease with the influenza which was endemic in France in previous years. The endemic disease has lacked the clinical feature of sudden onset and the epidemiologic feature of rapid spread. However, the exact time and place at which these features became sufficiently prominent to justify the recognition of an epidemic in France cannot be specified. On the whole, the evidence favors the conception of a gradual transition of influenza in France itself from the endemic to the epidemic form. Since 1890, influenza has remained endemic in many places and in nearly every country, and small epidemic outbreaks have been recognized from time to time. Given the essential conditions, the disease might have assumed epidemic proportions in any one of many different places and might have extended as a pandemic from such a point. The special condition favoring influenza in France, in addition to the ordinary

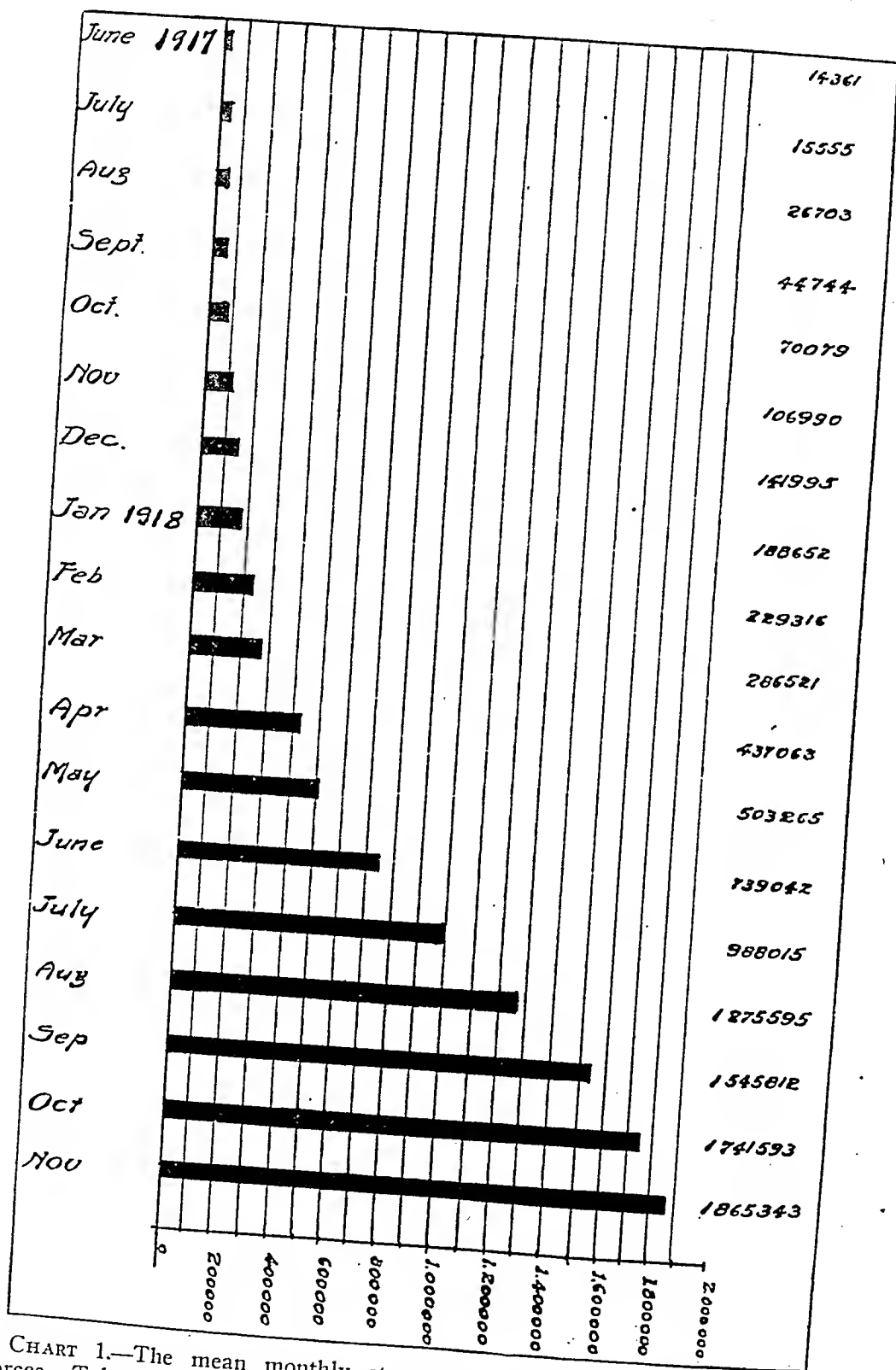


CHART 1.—The mean monthly strength of the American Expeditionary Forces. Taken from the records in the office of the Chief Surgeon. Note the sudden relative increase from March to April, 1918.

hardships of a country at war and the large amount of cold, damp weather, has been the fuel shortage, which has been peculiarly severe in France during the war. The evidence indicates that influenza has been very prevalent and that small epidemic outbreaks of it were recognized in the British Army in France in 1916 and in 1917. The arrival of American troops in France has been a factor of possible importance in relation to this disease. Their relative numbers are indicated in Tables 1 and 2 and Chart 1, the data of which apparently indicate line troops only, rather than the total forces. However, they are sufficient to give an idea of the relative increases. Attention may be directed to the sudden increase in mean strength from March to

TABLE 2.—DATA IN REGARD TO INFLUENZA AND PNEUMONIA. BY WEEKS

1918	Mean Strength A. E. F.	Influenza Cases	Influenza Deaths 100,000	Pneumonia Cases	Pneumonia Deaths 100,000	Pneumonia Deaths Number	Case Ratio
Week ending—							
July 5.....	38,579	1,118	122	187	15	4	1.0
12.....	40,714	1,247	124	115	10	11	1.1
19.....	1,008,438	917	30	116	10	14	1.4
26.....	1,100,449	715	68	120	6	20	2.7
August 2.....	1,112,486	637	31	127	12	23	1.9
9.....	1,214,461	1,250	124	130	10	15	1.5
16.....	1,235,496	1,233	110	130	11	26	2.3
23.....	1,215,522	1,173	92	121	4	24	2.1
30.....	1,222,522	1,538	121	114	10	32	2.2
September 6.....	1,476,885	1,516	115	126	11	33	2.5
13.....	1,520,320	2,007	212	479	23	123	14.8
20.....	1,570,771	4,271	273	471	30	121	21.1
27.....	1,624,722	2,671	241	571	35	119	21.9
October 4.....	1,772,122	2,235	352	1,005	33	301	33.1
11.....	1,723,125	3,375	421	1,033	31	314	41.1
18.....	1,711,573	2,081	313	1,223	73	122	33.1
25.....	1,726,519	1,632	311	1,200	109	1479	15.1
November 1.....	1,824,489	2,112	300	1,473	31	304	34.3
8.....	1,842,463	3,372	324	1,002	33	120	15.1
15.....	1,922,000	4,322	341	722	42	472	61.9
22.....	1,933,236	2,672	161	433	21	207	61.9
29.....	1,908,423	2,371	124	376	10	110	35.1

April, 1918, when 150,000 men were added to the 287,000 already in France. This increase of more than 50 per cent. required, in many places, the crowding of three or even four men into the quarters previously occupied by two, thus increasing enormously the opportunity for the rapid transmission of respiratory infection. Furthermore, it furnished a large group of newly arrived susceptible individuals and brought them into close association with the influenza already endemic among the American soldiers who had preceded them. One is tempted, therefore, to account for the origin of the epidemic by assuming an increase in virulence of endemic influenza, depending, first, on war conditions in France, especially the lack of fuel, second, on the introduction of Americans in 1917 and the spread of the disease among them during the following fall and winter, and third, the greater influx of susceptible American troops, beginning in the latter part of March,

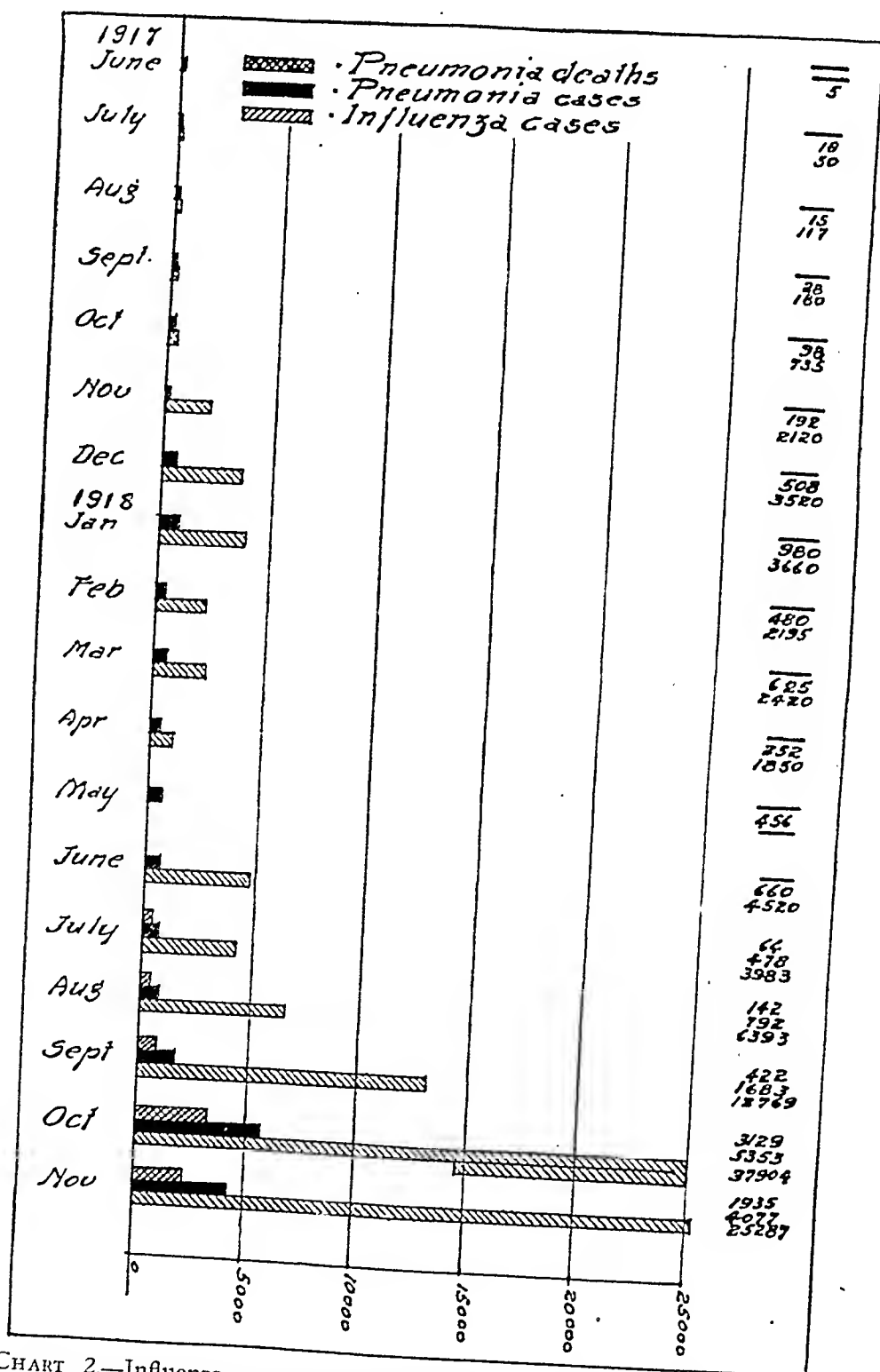


CHART 2.—Influenza cases, pneumonia cases and pneumonia deaths by months. The data for April and May are believed to be quite inaccurate because of incomplete tabulation of the statistics.

following which the disease assumed epidemic proportions. The evidence in favor of this conception appears strong, but a final decision should be withheld until reliable reports from the other European countries are at hand.

The number of cases of influenza and pneumonia reported in the A. E. F. are indicated in Chart 2, except for the month of May, for which the influenza figures are not available. In Chart 3 the rate for 100,000 mean strength is indicated for influenza and pneumonia. The remarkable feature is the high rate for influenza in November, December, 1917, and January, 1918, that of December being higher than in October, 1918, at the peak of the fall epidemic. Obviously, figures based on the reports of such a disease as influenza are only approximately accurate, but they have a relative value, nevertheless.

Pandemic Extension.—The spread of the epidemic from France to the United States by ships can hardly be questioned, although exact information in regard to this may better be obtained in America. Doubtless many of the transports carried the infection. A written report has been rendered in regard to one boat which had an outbreak of forty-two cases of influenza among the crew during the voyage to the United States in August, 1918. On its return to France this ship brought a part of the 64th Infantry. An epidemic of about 100 cases of influenza broke out on this boat again two days before reaching France, about September 1. The disease evidently spread rather rapidly in the United States, so that after September 15, nearly every transport arriving in France or in England, came in with a serious epidemic of influenza on board, which could be traced back to cases existing in the military organizations before embarkation in the United States. Reports from the United States indicate very clearly that the disease spread westward from the Atlantic seaboard.⁴ Although the disease must be regarded as identical in essential nature with influenza, which has been endemic in many parts of the United States since 1890, it is necessary to recognize that the virus brought over from France had acquired an epidemic quality to a degree which that previously existent in America no longer possessed.

An interesting example of transmission of the disease has been reported by Colonel M. A. Delaney from England. On August 26 and 27 the British vessel *Mantua*, which had influenza on board, stopped at Sierra Leone for consultation with two other British ships, *Chepstow Castle* and *Tahiti*, the former carrying New Zealand troops and the latter carrying naval ratings from East Africa. Influenza broke out

4. For further data as to influenza in the United States reference should be made to the article by Vaughan and Palmer in the *Military Surgeon*, October, 1918.

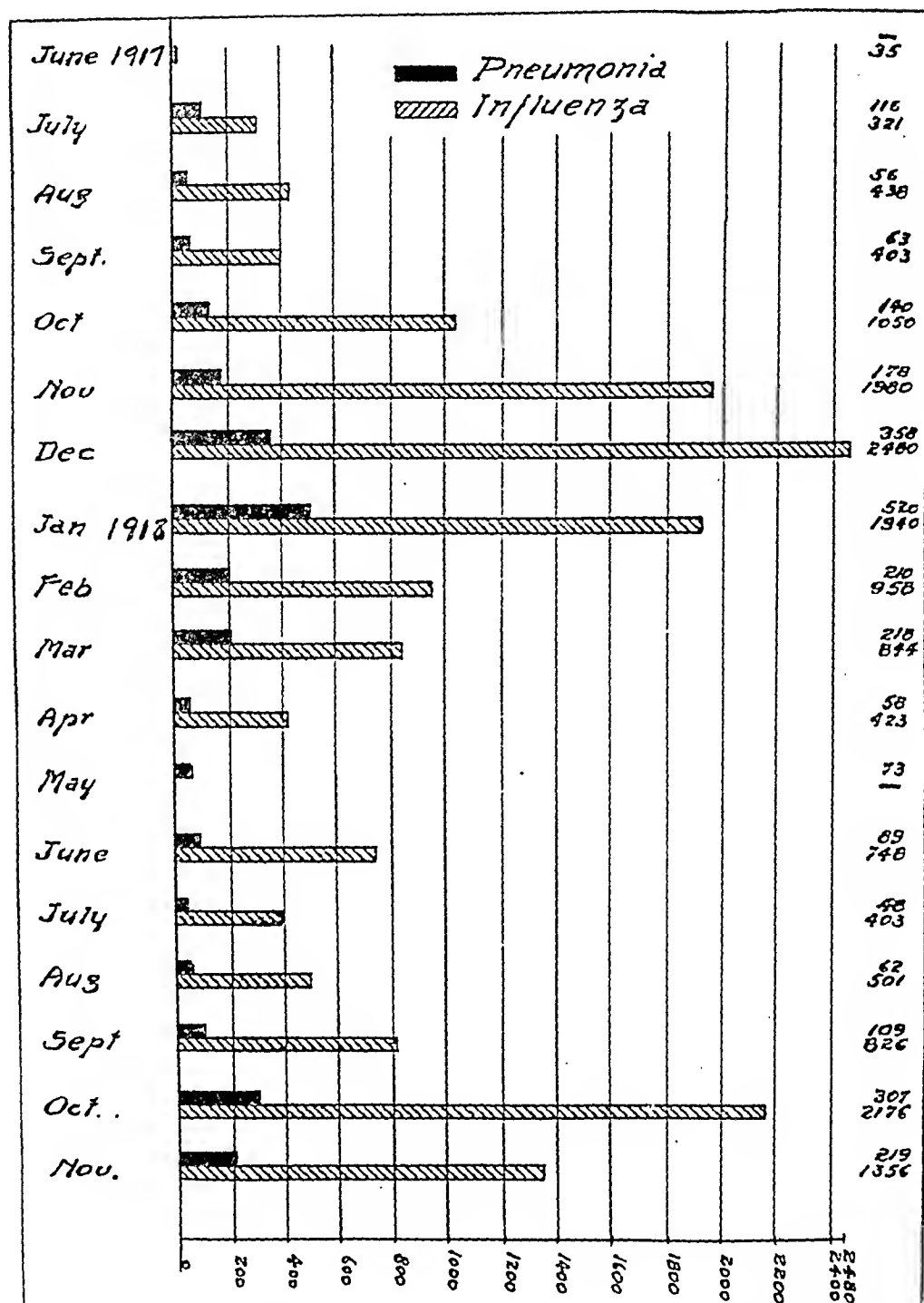


CHART 3.—Morbidity rate per 100,000 troops for influenza and pneumonia. Note that these diseases were relatively more prevalent in December, 1917, than at any time up to November, 1918.

on both the *Tahiti* and the *Chepstow Castle* within forty-eight hours after this call, and before arrival in England the *Tahiti* had sixty-eight deaths and the *Chepstow Castle* had thirty-eight. It is evident that New Zealand and East Africa had not been reached by the epidemic at the time of departure of these boats. On Oct. 23, 1918, the steamship *Mozambique* arrived at Lisbon from Cape Town, South Africa, having 200 deaths during the voyage and reporting an epidemic of influenza raging at Cape Town at the time of her departure.

SUMMARY

1. A disease, clinically recognized as influenza, became epidemic in the A. E. F. in France in May, 1918.

2. Since August, 1918, the epidemic, previously mild, has assumed a more malignant character, often leading to a fatal bronchopneumonia.

3. In the fatal cases the lungs have presented a picture of malignant coalescing bronchopneumonia, frequently with hemorrhagic tracheobronchitis. The changes have varied considerably according to chronicity of the disease and the nature of the secondary infections.

4. Influenza bacilli in large numbers have been found in the bronchi in fulminant cases. At most of the necropsies a mixture of bacteria was found in the respiratory tract, including pneumococci of various types, streptococci and sometimes staphylococci.

5. Blood cultures during life were usually negative, but showed pneumococci or streptococci in some cases.

6. Overwork, exposure to cold and wet, inadequate nourishment, poor ventilation, inhalation of dust and general physical discomfort have diminished the natural resistance to the disease.

7. The contagion spreads rapidly by distribution in the secretions of the nose and mouth, not only of the sick, but of many other infected persons not suffering from the disease.

8. The primary epidemic disease of the autumn is considered identical with that of the early summer, with the added complication of bronchopneumonia in the colder weather.

9. The bacillus of Pfeiffer is the apparent cause of the epidemic disease, but its causal relationship is not proved conclusively.

10. Rest in bed, warmth and bodily comfort, promptly enforced at the outset are the most important elements in the treatment.

11. Prophylaxis includes avoidance of contagion and general hygienic measures to enhance natural resistance and retain it at a high level. Vaccines are of questionable value.

12. Influenza has been endemic in France for many years, and during the war this infection appears to have assumed a more virulent type in this country, small epidemics having been recognized in the British army in the winter of 1916-17, and in the fall of 1917.

13. American troops in France suffered very much from influenza, especially in the winter of 1917-18, the disease apparently being the same as that which became epidemic in 1918.

14. The evidence suggests that the epidemic of influenza originated in France from the endemic influenza widely prevalent here. It is probable that the large numbers of American soldiers in France, subjected to strange environmental conditions, furnished a fertile soil for the propagation of the disease.

15. The epidemic was evidently carried by ships from Europe to the United States and to South Africa.

CONCLUSIONS

1. The epidemic of 1918 has been influenza.

2. It appears to have developed by transition from a widespread and serious endemic influenza in France.

303 East Twentieth Street.

THE RAPID CONSTRUCTION OF LIVER CELL PROTEIN ON A STRICT CARBOHYDRATE DIET CONTRASTED WITH FASTING

MECHANISM OF PROTEIN SPARING ACTION OF CARBOHYDRATE *

PAPER III

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SAN FRANCISCO

Problems of growth have interested numberless workers, especially during the past ten years. The growth of young animals as well as the growth of tumor cells has been investigated with great care, and attention has been directed to various food factors. We believe that most workers assume that the most rapid growth is to be found in malignant tumor development, which at times may exceed the speed of growth of the embryo or fetus.

We have been impressed with the great speed of repair of the normal liver following a type necrosis due to chloroform. Under such circumstances the formation of cell protoplasm proceeds with remarkable rapidity and exceeds any growth speed with which we are familiar. To illustrate in familiar figures—a healthy adult human of 75 kilograms, or 165 pounds, body weight, will possess a liver weighing approximately 1,700 gm. A suitable chloroform anesthesia during a fasting period will destroy one-half or more of this liver tissue, perhaps 800 gm. Under favorable circumstances complete repair can be effected in from seven to nine days—approximately 100 gm. per day, although the most rapid regeneration would develop during the third and fourth days, and might well exceed 150 gm. Formation of new tissue at a rate of 100 or 150 gm. per day means the construction of a mass of liver cells the size of the normal spleen or kidney *every twenty-four hours*. If this speed of growth should ever be attained by a malignant tumor it would give most astounding clinical histories—medullary cancers of the breast could grow to huge size in forty-eight hours, hypernephromas might attain their great size within a week or less, etc. This speed of growth on the part of a neoplasm would most assuredly command the respect, if not the admiration, of the surgeon. Yet the normal liver is capable of such speed of growth in reparative processes and can repeat this at frequent intervals as our experiments clearly show.

*From the George Williams Hooper Foundation for Medical Research, University of California Medical School.

It seems to us that this great capacity of the liver to repair and replace its injured cells gives the investigator a remarkable opportunity to study the rapid formation of large masses of new cell protoplasm under favorable circumstances, complicated by few confusing factors. The amount of injury can be accurately estimated, and if need be, controlled by removal of a bit of liver; the repair can be estimated with considerable accuracy by a similar operative removal of liver tissue, and the whole reaction takes place in a relatively short period of time, approximately between seven and fourteen days. It seems that this experimental method may be successfully applied to a number of important problems, some of which are merely touched on in our experiments.

"Protein sparing action of carbohydrate" is a familiar term to all workers in the field of metabolism. It is well known that this phenomenon is explained in two ways: (1) Protein is spared by carbohydrate at the *source* because the carbohydrate checks the normal or abnormal autolysis or katabolism of body protein; (2) protein is spared by carbohydrate through *conservation* of protein end-products which are fixed by the carbohydrate and made available for the construction in the body of new protein. Both of these hypotheses have a host of able supporters, but so far as we are aware the great bulk of the experimental evidence can be used with equal facility by an able advocate of either hypothesis. We believe that the experiments tabulated later give very positive support to the hypothesis of protein sparing by conservation of protein end-products. In our experiments a measurable amount of new body protein is constructed with the aid of a carbohydrate diet, but not during a fasting period. The cell protein break down, of course, is as great during fasting periods, and therefore an abundance of protein end-products are available, but the new liver cells are not formed in abundance unless carbohydrate is administered. The liver cell protoplasm must be formed in part from nitrogenous end-products which can only be derived from the injured liver cell protoplasm or the normal body protein katabolism. There is no nitrogen in the food. The new liver cells must be formed by an act of *conservation of protein split products* (for example, amino-acids) made possible by the abundant carbohydrate. We cannot understand how any amount of "protein sparing at the source" (decreased katabolism) could explain these findings.

Yet we do not wish to be understood as claiming that carbohydrates may not also spare protein at the source and inhibit autolysis or protein katabolism. Some experiments completed in this laboratory (unpublished) which deal with the regeneration of red blood cells in anemia would seem to indicate that carbohydrates under these experimental

conditions may actually protect the body protein from autolysis or katabolism. It is not impossible that carbohydrates may have both functions and may at times spare the proteins at the source, or, again, act by conservation of end-products. We submit these liver regeneration experiments, however, as positive evidence that under the conditions of the experiment the exhibition of a carbohydrate enables the body to build considerable amounts of new cell protein. This is positive evidence that carbohydrates *do act by conservation of protein split products*.

In the following communication (Paper IV) will be found some observations on fat feeding under these same conditions, and it will be noted that there are rather remarkable differences between liver regeneration as influenced by carbohydrate as compared with fat. The fat diet does not favor liver regeneration any more than does starvation. This point will be taken up again. Evidently fat does not favor the conservation of protein split products under the conditions of the experiment.

The metabolic disturbances following chloroform administration have received careful study for many years. In an article published in 1909, Howland and Richards,¹ among other things, recorded their observations on three dogs kept on starvation metabolism; a base line of two days was obtained, then prolonged chloroform anesthesia was given, sometimes repeated afterward. The total nitrogen excretion was found to rise on the day of anesthesia, higher on the second day (185 per cent. in one dog), and to continue high in the dogs that died, but to fall practically to normal in the dog that recovered. The curves of ammonia and urea excretion followed in a general way the total nitrogen curve.

Paton,² Lindsay,³ Marshall and Rowntree,⁴ and others, have studied the urinary nitrogen partition after chloroform injury, with somewhat variable results. Apparently the reaction varies with the intensity of injury.

Pearce⁵ after studying regenerative changes in the liver following experimental necrosis from hemagglutinative serum, ascribed the demonstrable differences in repair during the first two or three days to differences in initial injury, age, and general condition of the experimental animal.

1. Howland, J. and Richards, A. N.: J. Exper. M. 11:344, 1909.

2. Paton, D. N.: Proc. Royal Soc. Edinburgh 28:472, 1908.

3. Lindsay, D. E.: Biochem. J. 5:407, 1910-1911.

4. Marshall, E. K., and Rowntree, L. G.: J. Exper. M. 22:333, 1915.

5. Pearce, R. M.: J. M. Res. 15:99, 1906.

Beddard,⁶ in 1908, suggested the clinical use of glucose solutions following delayed chloroform injury. Weir,⁷ in 1909, reported the favorable use of glucose in a case of delayed chloroform poisoning. The use of sugar solutions in certain febrile diseases, such as typhoid, has a well recognized place in therapy.

The observations reported in this communication were begun in this laboratory by Hall and Whipple in connection with some work on experimental roentgen-ray intoxication. After chloroform anesthesia the nitrogen excretion rose tremendously, and in dogs kept on starvation generally remained high, but in those fed sugar it soon fell to the starvation, pre-anesthetic base line, or below. Several of these experiments included both a chloroform anesthesia, and a roentgen-ray exposure on the same animal; since this procedure complicated the curve of nitrogen excretion, the experiments in question are not included in the tables here presented.

METHODS

In experiments in which metabolism studies were made, the animals were confined in specially constructed cages; the urine collected in bottles beneath the cages; catheterization performed every twenty-four hours; and the cage urine, cage washings, catheterized urine, and bladder washings made up to a constant volume each day, and total nitrogen determinations made in duplicate by the Kjeldahl method. Blood urea, and total nonprotein nitrogen figures are recorded in milligrams per 100 c.c. of blood. Water and sugar solutions were given by stomach tube, except when vomiting was persistent, and such exceptions are noted in the protocols. Indicated operations were performed with aseptic precautions, under ether anesthesia, and the postoperative care was under constant supervision. The operative technic is described in more detail in Paper I of this series. By "fasting" we mean a discontinuance of food, but a liberal supply of water.

EXPERIMENTAL OBSERVATIONS

Table 10 includes experiments the protocols of which follow. We have considerable supplementary data, but some experiments are incomplete because of early death of the animals; others are complicated with severe distemper, roentgen-ray intoxication, etc.

Table 10 is intended for a brief, though comprehensive, summary of experiments, some of which show only an interesting nitrogen curve, while others are supplemented by microscopic liver findings. Estimates of liver necroses are very conservative, based on actual findings in comparable experiments, sometimes on the same animal.

6. Beddard, A. P.: *Lancet* 1:782 (March 4) 1908.

7. Weir, A. A.: *Lancet* 2:710 (Sept. 14) 1909.

TABLE 10.—METABOLISM FOLLOWING CHLOROFORM INJURY; LIVER REPAIR
UNDER CONDITIONS OF STARVATION AND SUGAR FEEDING

Experiment	Chloroform, Hours	Diet	Nitrogen Curve	Liver Injury	Liver Repair
70 (Dog 18-47)	1	Water before and for 10 days after chloroform, followed by 3 days on sugar	60% above starvation base line when sugar was added; fell to normal	Estimated 1/2 necrosis	
71 (Dog 18-89)	1½	Water before and for 2 days following chloroform; then sodium bicarbonate was added	Rose 30%; fell back to normal before sacrifice	4th day: over 1/2 necrosis; remainder fatty; repair started	11th day: 1/3 not repaired; fat +; calcium deposits present
72 (Dog 18-110)	1½	Water only.....	Rose 50%; fell back to starvation base line	5th day: 2/5 to 1/2 collapsed; remainder fatty	11th day: 1/3 to 2/5 still not repaired; fat ++; a few calcium deposits present
73 (Dog 18-105)	1¼	Water only	50% above base line on 9th day	3d day: 1/2 necrosis; fat in remainder	9th day: 1/4 not repaired; 2/3 fatty; atrophy
74 (Dog 18-49)	1	Water before and for 11 days after chloroform; sugar added for 6 days	99% above base line when sugar was added; fell at once, slightly below base line	Estimated 1/2 necrosis	
75 (Dog 18-49)	1	Sugar for 3 days before and 6 days after chloroform	Rose 110%, but began to fall on 3d day	Estimated 2/5 necrosis	
76 (Dog 18-49)	1½	Water + 5 gm. sodium bicarbonate daily	40% above base line at time of death	3d day: 3/5 necrosis; fat +	9th day: 1/3 to 2/5 not repaired; fat ++
77 (Dog 18-54)	1	Sugar before and after chloroform	Rose about 100%; fell to base line again by 8th or 9th day	Estimated 2/5 necrosis	
78 (Dog 18-54)	1	Water before and for 9 days following chloroform; sodium bicarbonate added for 2 days	60% above base line 12 days after chloroform	Estimated 1/2 necrosis	
79 (Dog 19-30)	1¼	Water only.....	2d day: 1/2 to 3/5 necrosis; remainder fatty	
80 (Dog 19-30)	1¼	Water before chloroform 100 gm. sugar daily for 8 days afterward	Rose about 126%; down practically to base line on 3d day; 2d rise	Estimated 1/2 to 2/5 necrosis (see Exper. 79)	8th day: 1/5 to 1/4 not repaired
81 (Dog 19-30)	1¼	Water only.....	Rose over 200%; practically back to base line on 7th day	Estimated 1/2 to 3/5 necrosis (see Exper. 79)	8th day: 1/4 not repaired; fat +
82 (Dog 19-39)	1¼	Water only.....	3d day: 1/2 to 3/5 necrosis; fat +; beginning resolution	
83 (Dog 19-39)	1¼	Water only.....	Rose about 20%; back to base line by 4th day; fell below	Estimated 1/2 to 3/5 necrosis (see Exper. 82)	7th day: 1/4 to 1/3 not repaired; fat +

TABLE 10.—METABOLISM FOLLOWING CHLOROFORM INJURY; LIVER REPAIR UNDER CONDITIONS OF STARVATION AND SUGAR FEEDING—(Continued)

Experiment	Chloroform, Hours	Diet	Nitrogen Curve	Liver Injury	Liver Repair
84 (Dog 19-39)	1¼	Sugar, 200 gm. daily for 7 days	Estimated 1/2 to 3/5 necrosis (see Exper. 82)	7th day: 1/5 not repaired; trace of fat; glycogen +++
85 (Dog 18-94)	1½	Water before and for 4 days following chloroform, sugar added for 3 days	Rose 100%; still 40% above base line when sugar was added; did not fully return on 3 days sugar	Estimated 1/2 to 3/5 necrosis	7th day: trace not repaired; slight congestion; glycogen ++
86 (Dog 18-121)	1¼	Water before chloroform; sugar daily afterward	Rose about 50%; below base line on 8th day	2d day: 2/5 to 1/2 necrosis; fat +	9th day: trace not repaired; trace of fat; glycogen +++
87 (Dog 18-82)	1½	Water before chloroform; sugar afterward	About 18% rise; back to base line on 3d day	Estimated 1/2 necrosis (see Exper. 40)	5th day: 1/4 not repaired; trace of fat; glycogen ++. 11th day: practically normal; glycogen ++
88 (Dog 18-124)	1¼	Starved 4 days; sugar and potatoes afterward	2d day: 2/5 necrosis; slight cell injury up to 1/2; trace of fat	7th day: repair practically complete; no fat; glycogen +++

EXPERIMENT 70.—*Fasting Metabolism; Chloroform Anesthesia; Later Sugar Diet.*—Dog 18-47, a small, brown and white male.

Date	Weight, Lbs.	Urine, C.c.	Nitrogen, Gm.	Diet	Remarks
Nov. 28	Water ad lib.	
Dec. 1	17.25	Bladder washed	400 c.c. water	
2	16.7	488	2.10	400 c.c. water	
3	16.0	571	1.93	400 c.c. water	
4	15.63	408	2.24	400 c.c. water	Speck of feces
4	Chloroform anesthesia for 1 hour (11:00-12:00)				
5	15.3	423	3.14	400 c.c. water	
6	14.94	445	3.81	400 c.c. water	Soft feces
7	14.44	474	3.42	400 c.c. water	Soft feces
8	14.3	366	3.58	400 c.c. water	Dog lively
9	14.06	453	3.75	300 c.c. water	
10	13.75	371	3.16	300 c.c. water	
11	13.5	385	3.19	300 c.c. water	
12	13.5	356	3.53	300 c.c. water	
13	13.44	265	3.42	300 c.c. water	
14	13.2	359	3.14	300 c.c. water	
15	12.75	412	3.64	300 c.c. water and 100 gm. sugar	
16	12.75	237	2.80	300 c.c. water and 100 gm. sugar	
17	12.7	322	2.21	300 c.c. sugar and 100 gm. sugar	
18	12.44	330	1.90	Mixed diet	Dog well.
Experiment discontinued					

EXPERIMENT 71.—*Fasting Metabolism; Chloroform Anesthesia; Sodium Bicarbonate Added.*—Dog 18-89, a young, tan female.

Date	Weight, Lbs.	Urine— Cath., C.c.	Cage, C.c.	Nitro- gen, Gm.	Diet	Remarks
Feb. 12	Water ad lib.	Dog normal
14	17.25	Bladder washed	350 c.c. water	
15	17.38	1	275	2.63	300 c.c. water	Feces —
16	17.9	0	255	2.21	300 c.c. water	
16	Chloroform anesthesia for 1½ hours (10:50-12:50)					
17	15.7	8	275	3.28	300 c.c. water	Quiet
18	15.5	0	235	3.78	300 c.c. water	Feces —
19	15.44	0	225	3.88	300 c.c. water	
					5 gm. NaHCO ₃	
					300 c.c. water	
20	15.2	0	310	3.92	5 gm. NaHCO ₃	
20	Piece of liver removed at 2:40 p. m.: over 1/2 necrotic; remainder fatty; repair started.					
21	14.38	0	350	3.65	300 c.c. water	Feces +; roundworms
					5 gm. NaHCO ₃	
22	14.3	1	155	3.49	300 c.c. water	
					5 gm. NaHCO ₃	
23	14.66	5	210	4.52	500 c.c. water	Bloody diarrhea: blood urea
					5 gm. NaHCO ₃	33 mg.; distemper
24	13.93	1	180	3.99	300 c.c. water	
					5 gm. NaHCO ₃	
25	13.3	0	210	3.63	500 c.c. water	Vomited
					5 gm. NaHCO ₃	
26	12.75	8	175	2.71	300 c.c. water	Feces +
					5 gm. NaHCO ₃	
27	12.9	3	270	2.71	300 c.c. water	Sacrificed at 10:00 a. m.: blood
					5 gm. NaHCO ₃	urea, 34 mg.

EXPERIMENT 71.—Dog 18-89. *Necropsy Report.*—Very much emaciated; operative wound open down to peritoneum; infected wound in groin; a few pustules over abdominal skin. *Liver:* weight, 173 gm.; finely mottled—hemorrhagic dots surrounded by white opaque areas. Abscess adjacent to liver wound. *Right kidney:* missing; left hypertrophied, with probable cloudy swelling.

Microscopic Report.—*Liver:* some repair has taken place, but still about one third unrestored; fat +; wandering cells and calcium deposits present in areas of repair. *Spleen:* fibrous. *Kidney:* slight cloudy swelling.

EXPERIMENT 72.—*Fasting Metabolism; Chloroform Anesthesia.*—Dog 18-110, a young, female collie.

Date	Weight, Lbs.	Urine— Cath., C.c.	Cage, C.c.	Nitro- gen, Gm.	Diet	Remarks
Mar. 22	25.58	Water ad lib.	Dog normal
25	22.56	Bladder washed	300 c.c. water	
26	22.25	0	240	3.83	300 c.c. water	
27	21.63	13	315	3.89	300 c.c. water	Feces —
28	21.18	1	235	3.11	300 c.c. water	
28	Chloroform anesthesia for 1½ hours (2:45-4:15 p. m.)					
29	20.5	2	250	2.83	300 c.c. water	Active
30	20.06	22	235	5.69	300 c.c. water	Feces +
31	19.9	5	150	5.30	300 c.c. water	Feces +
April 1	19.7	8	245	4.25	300 c.c. water	
2	19.3	1	250	2.95	300 c.c. water	
2	Piece of liver removed at 11 a. m.: 2.5 to 1.2 collapsed; fat to lobule peripheries					
3	19.2	16	100	3.11	300 c.c. water	Feces +
4	18.5	1	205	3.28	300 c.c. water	
5	18.5	25	280	3.94	300 c.c. water	Feces +
6	18.13	25	155	3.94	300 c.c. water	
7	17.94	15	210	3.48	300 c.c. water	Wound beginning to open

April 8: Ether and sacrifice; blood urea, 61 mg.

Necropsy Report.—Wound open. *Liver:* weight, 212 gm.; shows a fine dotting with red, each red dot being surrounded by a narrow opaque zone.

Stomach: slight hyperemia; *stomach* and *small intestine* contain partly digested blood; tape worms in ileum.

Microscopic Report.—*Liver*: one third to two fifths still not repaired; fat, ++; occasional calcium deposits present. *Kidneys*: slight congestion; slight cloudy swelling.

EXPERIMENT 73.—*Fasting Metabolism; Chloroform Anesthesia*.—Dog 18-106, an old, male fox terrier.

Date	Weight, Lbs.	Urine, Cath., C.c.	Urine, Cage, C.c.	Nitrogen, Gm.	Diet	Remarks
May 6	16.94	Water ad lib.	Dog normal
8	16.8	Bladder washed		200 c.c. water	
9	16.38	13	230	2.57	200 c.c. water	
10	16.2	13	220	2.14	200 c.c. water	
11	15.8	23	220	2.10	200 c.c. water	
11	Chloroform anesthesia for 1½ hours (11:00-12:15)					
12	15.3	27	160	2.57	200 c.c. water	Feces ++; sick
13	14.8	12	320	3.11	200 c.c. water	Feces +; blood urea, 46 mg.; vomited
14	15.25	16	160	3.47	200 c.c. water	
14	Piece of liver removed at 2:15; 1/2 necrotic; fat in remainder					
15	14.9	80	15	400 c.c. water in cage	Feces +; thirsty
16	14.9	17	380	4.20	500 c.c. water in cage	Feces +
17	14.3	54	455	5.06	500 c.c. water in cage	Wound opening; vomitus; jaundice
18	13.8	51	640	3.71	500 c.c. water in cage	Bile stained vomitus; very thirsty
19	13.56	6	440	3.40	600 c.c. water in cage	Vomiting
20	13.3	50	565	3.26	Vomiting; sacrificed at 10:30 a. m.

Necropsy Report.—Subcutaneous fat, and organs appear jaundiced. *Liver*: weight, 144 gm. Lobule centers are rather large and red, surrounded by wide opaque zones. Liver is speckled with small translucent patches; edge is irregularly atrophied. *Spleen*: shows two raised nodules, the size of peas, blotched red and gray. *Kidneys*: show no gross alterations, except jaundice. Near the tip of the left horn of the *uterus* is a firm, apparently fibrous, nodule the size of a large pea; on section this is found to be streaked yellow and white.

Microscopic Report.—*Liver*: Lobules two thirds fatty; central collapse of one fourth; portal fibrosis; lymph node shows breaking down red corpuscles. *Kidneys*: cloudy swelling. *Spleen*: fibrous; nodules are apparently spleno-lymphomas. Myoma in uterine horn.

EXPERIMENT 74.—*Fasting Metabolism; Chloroform Anesthesia; Sugar Added Later*.—Dog 18-49, a male fox terrier.

Date	Weight, Lbs.	Urine, C.c.	Nitrogen, Gm.	Diet	Remarks
Oct. 7	Water ad lib.	Dog normal
9	19.5	Bladder washed		400 c.c. water	
10	19.13	356	2.69	400 c.c. water	Solid feces
11	18.7	376	2.41	400 c.c. water	Solid feces
12	18.44	426	2.83	400 c.c. water	Slight diarrhea; blood NPN = 37 mg.
12	Chloroform anesthesia for 1 hour in p. m.				
13	18.7	450	4.26	400 c.c. water	Unable to catheterize; cage contained solid feces; dog active and well
14	17.5	399	4.99	400 c.c. water	Blood sample: nonprotein N = 36 mg.
15	17.0	422	3.73	400 c.c. water	
16	16.8	441	3.53	400 c.c. water	
17	16.38	455	4.09	400 c.c. water	Diarrhea

Date	Weight, Lbs.	Urine, C.c.	Nitrogen, Gm.	Diet	Remarks
Oct. 18	16.66	416	2.70	400 c.c. water	Dog well; blood nonprotein N = 42 mg.
19	15.75	426	3.56	400 c.c. water	
20	15.3	418	3.51	400 c.c. water	Unable to catheterize
21	15.0	440	3.92	400 c.c. water	
22	14.75	421	4.48	400 c.c. water	
23	14.2	451	5.49	400 c.c. water in a. m. 100 gm. sugar + kaolin in 200 c.c. water in p. m.	
24	14.13	691	4.23	100 gm. sugar	Diarrhea
25	13.94	459	2.83	400 c.c. water	
26	13.63	418	2.61	100 gm. sugar	Diarrhea
27	13.5	397	2.44	400 c.c. water	
28	13.3	424	2.30	100 gm. sugar	Diarrhea
29	13.66	404	2.24	400 c.c. water	
				Discontinued; dog active and apparently well, but emaciated

It will be noted in the foregoing experiments that the curve of nitrogen excretion following chloroform administration rises very sharply; where the animal is fasting, the output is usually much greater than when sugar is given, and the curve often does not come back to the former base line. This phenomenon of continued high output is illustrated graphically in Chart 1. In Experiments 70 and 74, sugar was given on the fourteenth day and a rapid drop of nitrogen excretion took place. The maximum daily output immediately referable to the chloroform usually occurred on the second day after anesthesia; the later rise in the second week, indicated in Chart 1, was, perhaps, due to pre-mortal breakdown of protoplasm. It is doubtful whether these curves would have dropped again had food not been given. This pre-mortal rise in nitrogen excretion of fasting animals occurs after a comparatively short period of starvation if chloroform anesthesia is administered during the course of the experiment.

Not all nitrogen curves remain above the metabolism base line after chloroform anesthesia, even though fasting is continued. Chart 2 shows two nitrogen elimination curves which come back to base line, or go below, and one curve for comparison which had not returned ten days after chloroforming. Operative procedures during the course of an experiment increase the nitrogen output to a certain extent. Curiously enough, Dog 18-89, used in Experiment 71, suffered a very severe injury, and repaired slowly and incompletely. Yet the curve of urinary nitrogen rises but moderately following the anesthesia and returns to the base line level within a few days. It is not safe to associate a high nitrogen excretion with extreme liver injury without proper control. This parallel is a common but not an invariable finding.

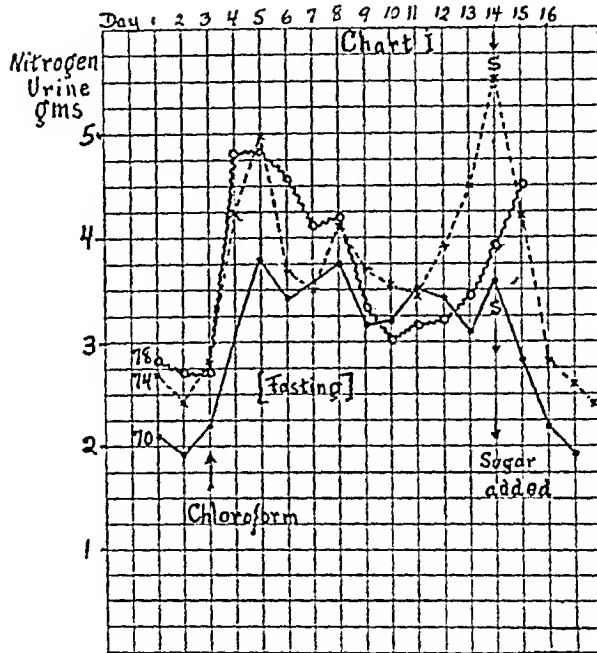


Chart 1.—Curve showing high output of nitrogen.

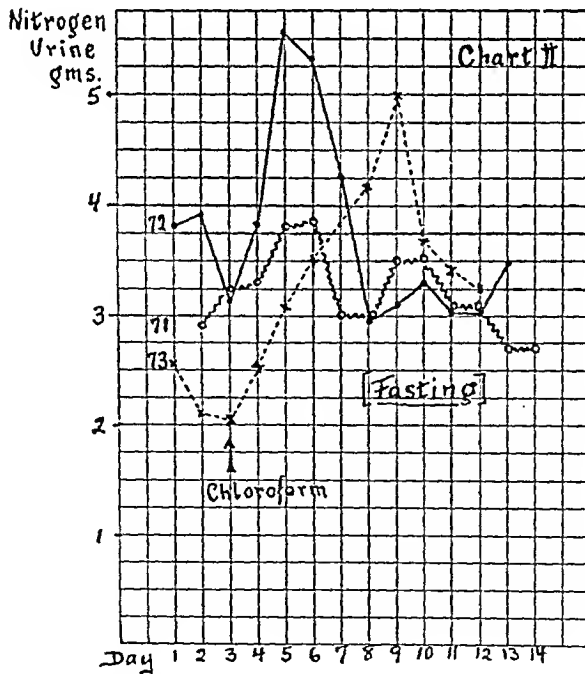


Chart 2.—Nitrogen elimination curves—two going back to base line or below, and one which had not returned to base line ten days after chloroform.

EXPERIMENT 75.—*Metabolism on Sugar Diet; Chloroform Anesthesia.*—Dog 18-49, a male fox terrier.

Date	Weight. Lbs.	Urine, C.c.	Nitrogen, Gm.	Diet	Remarks
Nov. 26	Water ad lib.	Dog normal
28	21.65	Bladder washed	100 gm. sugar + kaolin in 400 c.c. water	
29	20.9	318	2.02	100 gm. sugar + kaolin in 400 c.c. water	Soft feces
30	20.2	351	1.57	100 gm. sugar + kaolin in 400 c.c. water	Solid feces
Dec. 1	20.38	353	1.51	100 gm. sugar + kaolin in 400 c.c. water	Solid feces
1	Chloroform anesthesia for 1 hour (12:00-1:00)				
2	19.75	427	2.44	100 gm. sugar + kaolin in 400 c.c. water	Dog normal; very active
3	19.25	528	3.33	100 gm. sugar + kaolin in 400 c.c. water	Feces +; vomitus in bottle
4	19.3	221	2.35	100 gm. sugar + kaolin in 400 c.c. water	
5	18.75	391	1.55	100 gm. sugar + kaolin in 400 c.c. water	Diarrhea
6	18.56	241	1.95	100 gm. sugar + kaolin in 400 c.c. water	
7	18.25	367	Discontinued; soft feces

EXPERIMENT 76.—*Fasting Metabolism: Chloroform Anesthesia; Sodium Bicarbonate Added.*—Dog 18-49, a male fox terrier.

Date	Weight, Lbs.	Urine— Cath., Cage. C.c. C.c.		Nitro- gen, Gm.	Diet	Remarks
Apr. 10	22.56	Water ad lib.	Dog normal
13	22.0	Bladder washed	300 c.c. water: 5 gm. NaHCO ₃	
14	21.5	0	210	2.45	300 c.c. water: 5 gm. NaHCO ₃	Little soft, yellow feces
15	21.25	0	250	3.19	300 c.c. water: 5 gm. NaHCO ₃	Little soft, yellow feces
16	20.9	300 c.c. water: 5 gm. NaHCO ₃	
17	21.63	0	425	4.51	300 c.c. water: 5 gm. NaHCO ₃	Fed by mistake
18	20.38	1	395	2.57	300 c.c. water: 5 gm. NaHCO ₃	Soft feces
19	20.2	5	220	1.77	300 c.c. water: 5 gm. NaHCO ₃	Soft feces
19	Chloroform anesthesia for 1½ hours (10:10-11:40 a. m.); watery diarrhea					
20	18.75	3	350	3.02	600 c.c. water: 5 gm. NaHCO ₃	Not as active as usual; vomited
21	18.7	2	450	5.02	300 c.c. water: 5 gm. NaHCO ₃	Active
22	18.2	3	420	4.39	300 c.c. water: 5 gm. NaHCO ₃	Vomited
22	Piece of liver removed at 11 a. m.; 3/5 necrosis; fat +					
23	18.2	10	170	4.16	300 c.c. water: 5 gm. NaHCO ₃	Wound all right; feces +
24	3	380	5.51	600 c.c. water: 5 gm. NaHCO ₃	Vomited
25	17.75	4	170	5.09	300 c.c. water: 5 gm. NaHCO ₃	Vomited
26	17.06	2	340	3.72	200 c.c. water: 5 gm. NaHCO ₃	Vomited; feces +
27	16.25	2	255	3.35	200 c.c. water: 5 gm. NaHCO ₃	Wound slightly open
28	Found dead

Necropsy Report.—Hemorrhages subcutaneous (near wound), subpleural, and in thymus. Liver shows definite lack of repair; lobule centers are large and red; extending from the red centers to the lobule peripheries, the tissue is yellowish-white and opaque. Lymph nodes are large and dark. Cloudy swelling in heart and kidneys. Cystitis.

Microscopic Report.—Liver shows one third to two fifths collapsed stroma; more fat than at operation; phagocytized pigment. Pigment also in *spleen* and *lymph nodes*. Pseudomembrane in *stomach*. Cloudy swelling in *kidneys*.

EXPERIMENT 77.—*Metabolism on Sugar Diet; Chloroform Anesthesia.*—Dog 18-54, a white-eyed bull, female.

Date	Weight, Lbs.	Urine, C.c.	Nitrogen, Gm.	Diet	Remarks
Nov. 20	Water ad lib.	Dog very active
22	26.63	Bladder washed		100 gm. sugar + kaolin; 400 c.c. water	
23	26.5	191	2.38	100 gm. sugar + kaolin; 400 c.c. water	
24	26.38	231	2.072	100 gm. sugar + kaolin; 400 c.c. water	Feces ++
25	25.9	±	1.876	300 c.c. water; no sugar	
26	25.13	421	1.736	100 gm. sugar + kaolin; 400 c.c. water	
26	Chloroform anesthesia for 1 hour (10:--11:00 a. m.)				
27	24.63	416	3.36	100 gm. sugar + kaolin; 400 c.c. water	
28	24.06	426	3.018	100 gm. sugar + kaolin; 400 c.c. water	Feces ++
29	24.06	210	2.24	100 gm. sugar + kaolin; 400 c.c. water	
30	23.56	500	2.072	100 gm. sugar + kaolin; 400 c.c. water	
Dec. 1	23.63	247	2.38	100 gm. sugar + kaolin; 400 c.c. water	Diarrhea
2	23.3	357	2.10	100 gm. sugar + kaolin; 400 c.c. water	
3	23.0	398	2.072	100 gm. sugar + kaolin; 400 c.c. water	Diarrhea
4	22.7	386	2.016	100 gm. sugar + kaolin; 400 c.c. water	Diarrhea
5	22.38	388	1.792	100 gm. sugar + kaolin; 400 c.c. water	Soft feces
6	22.06	431	1.736	100 gm. sugar + kaolin; 400 c.c. water	Soft feces
7	21.63	467	Soft feces
	Experiment discontinued				

Chart 3 illustrates the usual nitrogen elimination obtained by feeding sugar to animals anesthetized with chloroform. In two cases sugar feeding was begun before chloroform was administered, and in two cases afterwards. If the sugar feeding was intensive, one might expect a protective action against liver injury, but in Experiments 75 and 77 there was a preliminary fasting period, and the feeding was probably inadequate to furnish complete protection to an adult animal. We should expect, therefore, a certain amount of liver injury in all these cases. The average rise in the nitrogen curve is somewhat less than that obtained in the fasting experiments. At first sight, Experiment 86 appears to have an enormously increased output, but when it is observed at what level the chloroform was given, it will be seen that the actual rise was less than a 50 per cent. increase. Why the elimination in this case was so much greater on the second and third days than on the first day of the experiment is hard to explain; perhaps intercurrent infection caused the sudden increase. It will be readily seen that these curves come back to the metabolism base line following chloroform.

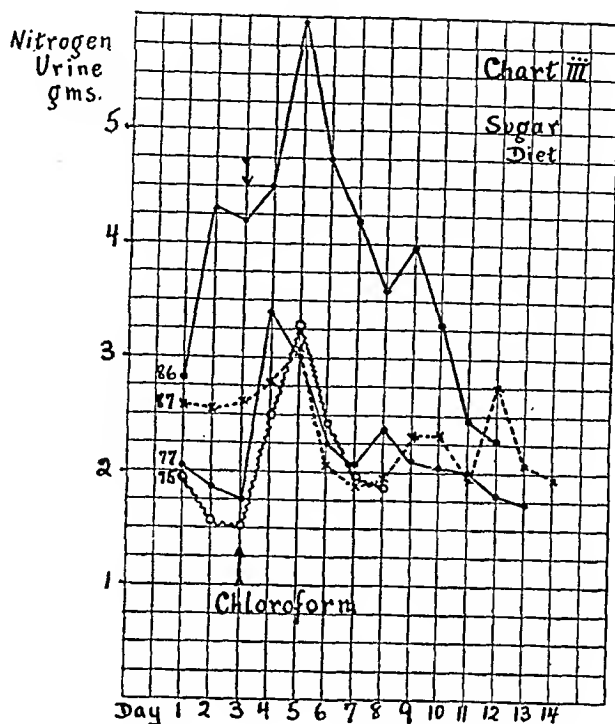


Chart 3.—Usual nitrogen elimination by sugar fed animals after chloroform.

EXPERIMENT 78.—*Fasting Metabolism; Chloroform Anesthesia.*—Dog 18-54, a female bull.

Date	Weight, Lbs.	Urine Cath., C.c. C.c.		Nitro- gen, Gm.	Diet	Remarks
Jan. 28	29.13	Water ad lib.	Dog normal
29	Water ad lib.	
30	27.9	Bladder washed		300 c.c. water	
31	27.06	8	260	2.78	400 c.c. water	
Feb. 1	26.94	5	440	2.69	400 c.c. water	
2	26.3	6	440	2.78	400 c.c. water	
3	25.0	37	495	4.79	400 c.c. water	Feces +; very active
4	24.5	10	475	4.92	400 c.c. water	Feces +
5	24.25	25	345	4.56	400 c.c. water	
6	23.75	3	410	4.10	400 c.c. water	
7	23.44	17	365	4.12	400 c.c. water	
8	23.13	10	415	3.26	400 c.c. water	
9	22.7	7	440	2.99	400 c.c. water	
10	22.25	0	425	3.16	400 c.c. water	
11	22.0	11	470	3.21	400 c.c. water	Feces +
12	21.38	0	375	3.45	400 c.c. water; 5 gm. NaHCO ₃	Diarrhea
13	21.3	6	275	3.92	400 c.c. water 5 gm. NaHCO ₃	
14	20.8	12	440	4.50	Extra food	Metabolism discontinued

EXPERIMENT 79.—*Simple Starvation and Chloroform Anesthesia.*—Dog 19-30, a black and white male terrier.

Oct. 4: Wt., 21.06 lbs. Isolated for *starvation* before daily feeding; healthy and active.

Oct. 5: Wt., 20.7 lbs.; Oct. 6, wt., 20.11 lbs.; no food.

Oct. 7: Wt., 20.06 lbs. *Chloroform anesthesia* for one and a quarter hours (from 9:50 to 11:05 a. m.).

Oct. 8: Wt., 19.7 lbs. Dull; gave food, but none eaten .

Oct. 9: Wt., 19.5 lbs. Brighter; sugar by stomach tube. *Piece of liver removed* at 3 p. m.; sections show one half to three fifths necrosis, with fat to lobule peripheries.

Oct. 10 to 12: Dog dangerously sick; gave glucose solution intravenously on four occasions. Slow recovery.

EXPERIMENT 80.—*Metabolism on Sugar Diet After Chloroform Anesthesia.*
—Dog 19-30, a black and white, male terrier.

Date	Weight, Lbs.	Urine— Cath., Cage, C.c.		Nitro- gen, Gm.	Diet	Remarks
Nov. 10	21.2	Water ad lib.	Dog normal
11	20.5	Bladder washed		200 c.c. water	Feces +
12	20.06	2	250	1.31	200 c.c. water	Blood clots in blad- der washings
13	19.56	3	240	1.08	200 c.c. water	Blood clots in blad- der washings
13	Chloroform anesthesia for 1½ hours (10:00-11:15 a. m.)					
14	19.0	8	250	1.79	a. m.: 100 gm. cane sugar; 200 c.c. water p. m.: 100 gm. cane sugar; 200 c.c. water	Vomited
15	18.44	6	595	2.37	a. m.: 100 gm. sugar; 100 c.c. water + kaolin p. m.: 200 c.c. water	
16	18.5	0	215	1.33	a. m.: 100 gm. sugar; 100 c.c. water + kaolin p. m.: 200 c.c. water	Feces ++
17	18.5	4	210	1.35	a. m.: 100 gm. sugar; 100 c.c. water + kaolin p. m.: 200 c.c. water	Feces ++
18	18.5	2	200	1.48	a. m.: 100 gm. sugar; 100 c.c. water + kaolin p. m.: 200 c.c. water	Feces ++
19	18.3	1	225	1.54	a. m.: 100 gm. sugar; 100 c.c. water + kaolin p. m.: 200 c.c. water	Feces ++
20	18.0	2	200	1.62	a. m.: 100 gm. sugar; 100 c.c. water + kaolin p. m.: 200 c.c. water	Feces ++
21	17.75	2	340	1.57	Water ad lib.	Metabolism dis- continued
21	Piece of liver removed at 4 p. m.; 1/5 to 1/4 not filled out; fat + in lobule centers					

EXPERIMENT 81.—*Fasting Metabolism; Chloroform Anesthesia.*—Dog 19-30, a black and white, male terrier.

Date	Weight, Lbs.	Urine— Cath., Cage, C.c.		Nitro- gen, Gm.	Diet	Remarks
Dec. 3	19.3	Water ad lib.	Dog normal
4	18.75	Bladder washed		200 c.c. water	
5	18.3	5	305	1.53	200 c.c. water	
6	17.94	3	75	1.44	400 c.c. water in cage	
6	Chloroform anesthesia for 1½ hours (9:40-10:55 a. m.)					
7	17.56	23	170	2.64	400 c.c. water in cage	Sick; vomited
8	17.06	7	540	1.48	400 c.c. water in cage	Weak; thirsty
9	17.0	20	325	5.21	170 c.c. water	
10	16.56	3	290	3.67	200 c.c. water in cage	Vomited
11	16.13	7	350	2.63	200 c.c. water in cage?	Feces +
12	15.94	0	600	1.81	300 c.c. water in cage	
13	15.5	4	310	1.64	200 c.c. water in cage	
14	15.44	2	190	1.62	Water ad lib.	Metabolism discontinued
14	Piece of liver removed at 10:30 a. m. Sections show liver 1/4 unrepaid; fat +					

Chart 4 shows the difference in nitrogen elimination following chloroform, in two experiments on the same dog; in Experiment 80 sugar diet was given, in Experiment 81 the animal fasted throughout. The pre-anesthetic treatment was the same in both cases, and presumably the injuries sustained were practically equal. Both curves came back almost to base line, and at the time of discontinuing the experiments the daily nitrogen elimination figures were the same. The striking difference in the two curves is in the amount of nitrogen excreted. The small curve in Experiment 80 can only be due to the single variable—sugar feeding. This suggests very strongly that some of the necrotic liver end-products were held in the body by the ingested sugar, perhaps for construction of new liver parenchyma.

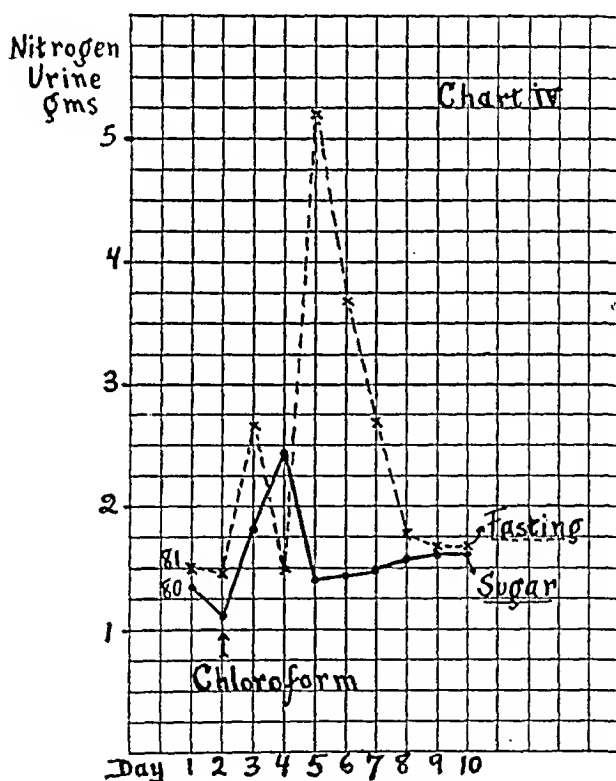


Chart 4.—Curves showing difference in nitrogen elimination following chloroform in two experiments on the same dog. In one (experiment 80) sugar diet was given; in the other (experiment 81) the animal fasted throughout.

EXPERIMENT 82.—*Simple Starvation and Chloroform Anesthesia.*—Dog 19-39, a female Airdale.

Oct. 8: Wt., 26.13 lbs. Isolated before daily feeding; *starvation*; has recovered from distemper; in good condition.

Oct. 9: Wt., 25.75 lbs.; Oct. 10, wt., 24.8 lbs.; no food.

Oct. 11: Wt., 24.5 lbs. Active and healthy. *Chloroform anesthesia for one and a quarter hours* (from 5:50 to 7:05 p. m.).

Oct. 12: Wt., 23.06 lbs. Still bright and active.

Oct. 13: Wt., 22.9 lbs. Still bright and active.

Oct. 14: Wt., 22.75 lbs. *Piece of liver removed* at 9:30 a. m. Sections show one half to three fifths necrosis (beginning resolution); fat + (scattered). Mixed diet.

EXPERIMENT 83.—*Fasting Metabolism; Chloroform Anesthesia.*—Dog 19-39, a female Airdale.

Date	Weight, Lbs.	Urine— Cath., C.e. Cage, C.e.		Nitro- gen, Gm.	Diet	Remarks
Oct. 28	24.44	Water ad lib.	Dog normal
29	23.56	Bladder washed		250 c.c. water	
30	23.06	21	220	2.74	250 c.c. water	
31	23.0	46	190	2.85	250 c.c. water	Feces +
Nov. 1	22.5	102	155	3.70	Chloroform anesthesia for 1½ hours (1:10-2:25 p. m.)	
					250 c.c. water,	Quiet; vomited
					100 c.c. in cage	
2	22.13	112	20	3.48	200 c.c. water	
3	21.8	87	130	2.92	220 c.c. water	
4	21.56	5	220	2.88	200 c.c. water	
5	21.3	0	170	2.18	200 c.c. water	
6	21.06	11	250	2.27	200 c.c. water	
7	21.0	23	250	2.27	Metabolism discontinued; mixed diet
7	Piece of liver removed at 2:30 p. m.; from 1/4 to 1/3 not repaired; fat +; congestion					

EXPERIMENT 84.—*Regeneration on Sugar Diet.*—Dog 19-39, a female Airdale.

Dec. 20: Wt., 27.3 lbs. Isolated for *starvation* before daily feeding; wounds all healed; bright and active.

Dec. 21 to 22: No food.

Dec. 23: Wt., 25.2 lbs. Bright and very active. *Chloroform anesthesia for one and a quarter hours* (from 9:15 to 10:30 a. m.).

Dec. 24: Wt., 24 lbs. Very active; apparently not affected by chloroform; 200 gm. *cane sugar* by stomach tube.

Dec. 25 to 27: 200 gm. *sugar* daily; retained all right.

Dec. 28: Wt., 22 lbs. Very active; vomited; put 200 gm. *sugar* in solution in cage; taken and retained.

Dec. 29: Wt., 21.8 lbs. *Sugar* (200 gm.) left in cage.

Dec. 30: Wt., 21.5 lbs.; 200 gm. *sugar* in a. m. *Piece of liver removed* at 4:30 p. m. Sections show good repair; a little central stroma not filled out (one fifth or less); mere trace of fat; glycogen + + +. Mixed food.

EXPERIMENT 85.—*Fasting Metabolism; Chloroform Anesthesia; Sugar Added Later.*—Dog 18-94; a tan male bull.

Date	Weight, Lbs.	Urine— Cath., C.e. Cage, C.e.		Nitro- gen, Gm.	Diet	Remarks
Feb. 28	17.0	Water ad lib.	Dog, young; normal
Mar. 4	15.3	Bladder washed		250 c.c. water	Feces
5	15.0	4	210	1.85	250 c.c. water	
6	14.56	0	280	2.11	250 c.c. water	Sore eyes; distemper?
7	14.44	0	200	2.12	250 c.c. water	
7	Chloroform anesthesia for 1½ hours (10:15-11:45 a.m.)					
8	13.8	6	280	3.65	250 c.c. water	Quiet
9	13.38	1	260	4.34	250 c.c. water	Distemper
10	13.3	0	190	3.28	250 c.c. water	
11	13.25	6	305	3.00	250 c.c. water	Trace of blood per catheter
12	12.5	0	240	2.94	200 c.c. water;	Vomited
					100 gm. sugar	
13	11.8	6	365	2.66	200 c.c. water;	Feces +; blood in washings;
					100 gm. sugar	weak and sick
14	11.56	10	140	2.57	200 c.c. water;	Feces +; distemper worse; sac-
					100 gm. sugar	rificed in p.m.; blood urea 37 mg.

Necropsy Report.—Lungs show some dark areas, probably early pneumonia, especially in right lower lobe. *Liver:* delicate dimpling, and stippling with red. *Kidneys:* cloudy swelling, ecchymoses in outer cortex. Slight cystitis.

Microscopic Report.—Lungs: atelectasis; spots of cell infiltration. *Spleen:* hemorrhages. *Liver:* slight unrestored central collapse, with congestion and wandering cell reaction; glycogen +. *Kidneys:* cloudy swelling; hyalin casts; congestion; hemorrhage.

EXPERIMENT 86.—*Metabolism on Sugar Diet; Chloroform Anesthesia.*—Dog 18-121, a young, female collie.

Date	Weight, Lbs.	Urine		Nitro- gen, Gm.	Diet	Remarks
		Cath., C.c.	Cage, C.c.			
May 6	28.13	Water ad lib.	Dog normal
7	Water ad lib.	
8	26.0	Bladder washed		300 c.c. water in cage	
9	25.94	0	50	2.8	300 c.c. water, stomach tube	Trace of blood in urine during experiment
10	25.25	7	280	4.31	300 c.c. water, stomach tube	
11	24.75	2	290	4.20	25 gm. glucose; 75 gm. cane sugar + kaolin; 300 c.c. water	Vomited a little
11	Chloroform anesthesia for 1½ hours (11:00-12:15)					
12	23.75	0	560	4.51	25 gm. glucose; 75 gm. cane sugar + kaolin; 300 c.c. water	Feces +; active
13	23.25	0	490	6.06	25 gm. glucose; 75 gm. cane sugar + kaolin; 300 c.c. water	Vomited some; blood urea 41 mg.
13	Piece of liver removed at 11:15 a. m.; 2/5 to 1/2 necrosis; fat +					
14	22.5	0	290	4.99	25 gm. glucose; 75 gm. cane sugar + kaolin; 300 c.c. water in cage	
15	22.56	1	125	4.17	25 gm. glucose; 75 gm. cane sugar + kaolin; 300 c.c. water in cage	Feces +
16	22.5	0	80	3.58	25 gm. glucose; 75 gm. cane sugar + kaolin; 300 c.c. water in cage	Wound opening
17	22.13	1	105	4.00	25 gm. glucose; 75 gm. cane sugar + kaolin; 300 c.c. water, stomach tube and cage	Diarrhea
18	21.75	0	380	3.30	25 gm. glucose; 75 gm. cane sugar + kaolin; 300 c.c. water, stomach tube and cage	Feces +
19	21.8	0	80	2.42	25 gm. glucose; 75 gm. cane sugar + kaolin; 300 c.c. water, stomach tube and cage	Wound open
20	22.0	1	90	2.24	Sacrificed at 10 a. m.; blood urea 23 mg.

Necropsy Report.—Open incision is walled off by omentum; adhesions to liver in region of wound. *Liver:* weight, 327 gm.; lobule centers are unusually distinct; perhaps a trace of fat; bladder mucosa is quite injected in patches.

Microscopic Report.—Liver: a mere trace of central stroma not filled out; trace of fat; glycogen very heavy throughout.

EXPERIMENT 87.—*Metabolism on Sugar Diet; Chloroform Anesthesia.*—Dog 18-82, a young, white, female bull.

Date	Weight, Lbs.	Urine, Cath., C.c.	Cage, C.c.	Nitrogen, Gm.	Diet	Remarks
Mar. 21	22.0	Water ad lib.	Dog normal
25	18.44	Bladder washed		...	200 c.c. water	Pus in urine
26	17.94	1	225	2.50	250 c.c. water	Blood and pus in urine; vomited
27	17.25	0	205	2.57	200 c.c. water	Feces +
28	17.13	1	220	2.61	25 gm. glucose; 100 gm. cane sugar + kaolin; 200 c.c. water	Pus in washings
28	Chloroform anesthesia for 1½ hours (2:45-4:15 p. m.)					
29	16.9	2	100	2.79	25 gm. glucose; 100 gm. cane sugar + kaolin; 200 c.c. water	
30	16.5	3	90	3.09	25 gm. glucose; 100 gm. cane sugar + kaolin; 200 c.c. water	
31	16.06	0	65	2.13	25 gm. glucose; 100 gm. cane sugar + kaolin; 200 c.c. water	Feces +
Apr. 1	16.2	0	70	1.84	25 gm. glucose; 100 gm. cane sugar + kaolin; 200 c.c. water	
2	15.9	1	105	2.09	25 gm. glucose; 100 gm. cane sugar + kaolin; 200 c.c. water	Feces +; vomited some
2	Piece of liver removed at 12 m.; about 1/4 collapsed; trace of fat; glycogen ++					
3	15.44	4	275	2.38	25 gm. glucose; 100 gm. cane sugar + kaolin; 200 c.c. water	
4	15.5	1	60	2.40	25 gm. glucose; 100 gm. cane sugar + kaolin; 200 c.c. water	Feces ++; pus in washings
5	15.38	1	95	2.06	25 gm. glucose; 100 gm. cane sugar + kaolin; 200 c.c. water	Feces +
6	15.13	1	130	2.78	25 gm. glucose; 100 gm. cane sugar + kaolin; 200 c.c. water	Vaginal discharge; feces +
7	15.2	0	60	2.13	25 gm. glucose; 100 gm. cane sugar + kaolin; 200 c.c. water	Feces +; vaginal discharge
8	15.0	2	165	1.94	Bread and milk	Feces +; wound open
8	Piece of liver removed at 10:30 a. m.; practically normal; glycogen ++					

EXPERIMENT 88.—*Regeneration on Sugar and Potatoes.*—Dog 18-124, a young, black and white female.

Aug. 22: Wt., 12.63 lbs. *Chloroform anesthesia for one and a quarter hours* (from 2:25 to 3:40 p. m.); previous thyroid feeding for four days. (See experiment 23.)

Aug. 23: Wt., 13 lbs. Active; gave 20 gm. glucose and 80 gm. cane sugar + kaolin in 150 c.c. water by stomach tube; *potatoes ad lib.* Piece of liver removed at 10:30 a. m. Sections show two fifths necrosis, and slight surrounding cell injury up to one half; very little fat.

Aug. 25: Wt., 12.63 lbs. Active; 100 gm. sugar + potatoes ad lib.

Aug. 26: Wt., 12.63 lbs.; Aug. 27, wt., 12.60 lbs.; sugar and potatoes as before.

Aug. 28: Wt., 12.44 lbs. Wound opening up a little; food as before.

Aug. 29: Wt., 12.2 lbs. Very active; potatoes, but no sugar. Piece of liver removed at 2 o'clock, sections show practically complete repair; no fat; glycogen in large amount.

The attempt has been made in Table 11 to bring together in comparative form the experiments relating to regeneration on starvation and sugar diets, in which we have more or less complete histologic data.

TABLE 11.—SUMMARY OF LIVER INJURY AND REPAIR

Fasting	Sugar Diet
Experiment 73, Dog 18-106 Fasted 5 days before chloroform anesthesia 1½ hours Injury on 3d day: 1/2 necrosis; fat in remainder Repair on 9th day: 1/4 not repaired; 2/3 fatty	Experiment 86, Dog 18-121 Fasted 5 days before chloroform anesthesia, 1½ hours Injury on 2d day: 2/5 to 1/2 necrosis; fat moderate Repair on 9th day: trace not repaired; trace of fat; glycogen ++
Experiment 72, Dog 18-110 Fasted 7 days before chloroform anesthesia, 1½ hours Injury on 5th day: 2/5 to 1/2 collapsed; fat to periphery Repair on 11th day: 1/3 to 2/5 still not repaired; fat ++; a few calcium deposits present	Experiment 87, Dog 18-82 Fasted 7 days before chloroform anesthesia, 1½ hours Injury on 5th day: 1/4 collapsed; trace of fat; glycogen +; another experiment (Exper. 40) on same dog shows 1/2 initial necrosis Repair on 11th day: practically normal; glycogen ++
Experiment 76, Dog 18-49 Fasted (+ NaHCO ₃) for 9 days before 1½ hours chloroform anesthesia Injury on 3d day: 3/5 necrosis; fat + Repair on 9th day: 1/3 to 2/5 not repaired; fat ++	Experiment 85, Dog 18-94 Fasted 8 days before 1½ hours chloroform anesthesia; fasted 4 days after chloroform, then sugar for 3 days Injury estimated 1/2 to 3/5 necrosis Repair on 7th day: trace not repaired; glycogen ++
Experiment 71, Dog 18-89 Fasted 5 days before 1½ hours chloroform anesthesia; given NaHCO ₃ later Injury on 4th day: over 1/2 necrosis; remainder fatty; repair started Repair on 11th day: 1/3 not repaired; fat +; calcium deposits present	Experiment 88, Dog 18-124 3 gm. thyroid powder daily for 4 days previous to 1½ hours chloroform anesthesia Injury on 2d day: 2/5 necrosis; severe injury up to 1/2; potatoes added to sugar diet Repair on 7th day: practically complete repair; no fat; glycogen +++
Experiment 81, Dog 19-30 Fasted 4 days before 1¼ hours chloroform anesthesia Injury estimated 1/2 to 3/5 necrosis—from control experiment on same dog (see Exper. 79) Repair on 8th day: 1/4 not repaired; fat +	Experiment 80, Dog 29-30 Fasted 4 days before 1¼ hours chloroform anesthesia Injury estimated 1/2 to 3/5 necrosis (see control Exper. 79) Repair on 8th day: 1/5 to 1/4 not repaired; repair is slightly, though distinctly better than in Exper. 81
Experiment 83, Dog 19-39 Fasted 4 days before 1¼ hours chloroform anesthesia Injury estimated 1/2 to 3/5 necrosis—from control experiment on same dog (see Exper. 82) Repair on 7th day: 1/4 to 1/3 not repaired; fat moderate	Experiment 84, Dog 19-39 Fasted 4 days before 1¼ hours chloroform anesthesia Injury estimated 1/2 to 3/5 necrosis (see control Exper. 82) Repair on 7th day: about 1/5 not repaired; trace of fat; glycogen +++

We have observed that two successive chloroform injuries in the same dog are practically the same, the starvation period, the duration of anesthesia, and other variables being equal. Operations during the course of an experiment introduce certain complications. Therefore, we decided to determine the injuries in some dogs under standard conditions of four days' starvation and one and a fourth hours' chloroform anesthesia, and thereafter to use these dogs for metabolism work, assuming that their injuries were comparable to the controls in each instance, and to operate only at the end of an experiment to find out the amount of repair. Experiments 80 and 81 on Dog 19-30, and Experiments 83 and 84 on Dog 19-39, are examples of this plan.

The evidence here tabulated overwhelmingly demonstrates a greater regeneration on a carbohydrate diet than on starvation. This difference is usually more striking when the sections are compared than when estimations of the injuries are set down in figures. In successive experiments on the same dog, this difference in repair can be correlated with a difference in nitrogen elimination (Chart 4), the fasting dog usually excreting far more nitrogen than the sugar fed animal. The obvious conclusion is that part of the ingested sugar, plus the nitrogen which would otherwise be eliminated, goes to form new liver tissue.

DISCUSSION

Through the efforts of Lusk,⁸ and others, the phenomenon of "protein sparing action of carbohydrate" is well recognized. That is, the loss of nitrogen in fasting is much less if the body contains a good store of glycogen, and the loss of nitrogen on an insufficient protein intake may be lessened or perhaps stopped by the addition of a suitable amount of carbohydrate (or fat) to the diet. Carbohydrate added to a diet already maintaining nitrogen equilibrium not only causes a delay in nitrogen excretion,⁹ but may actually induce a storage of protein in the body.¹⁰

It is recognized that carbohydrates in the ordinary body metabolism furnish fuel for heat and energy. A fairly definite percentage of sugar is maintained in the blood stream, and within certain limits extra sugar is stored as glycogen, or converted to fat, for future use as fuel. Under certain circumstances, for example, prolonged fasting, or pathologic conditions such as diabetes, the proteins are burned up, and it is known that about 60 per cent. of tissue protein can be made available as carbohydrate.

The probability that lactic acid, and perhaps pyruvic acid, may be intermediate products in carbohydrate metabolism has been recognized for years. Chemically, these two acids are quite closely allied to certain amino-acids, notably alanin.¹¹ Ringer, Frankel and Jonas¹² have shown that lactic acid, alanin, and to a less extent pyruvic acid, are capable of yielding glucose in phlorizinized dogs. Kocher¹³ has demonstrated that lactic acid, and to a less extent pyruvic acid, are "protein sparsers."

8. Lusk, Graham: *The Elements of the Science of Nutrition*, Ed. 3, 1917.

9. Mendel, L. B., and Lewis, R. C.: *J. Biol. Chem.* **16**:37, 1913-1914.

10. Sherman, H. C.: *Chemistry of Food and Nutrition*, Ed. 2, Macmillan Company, New York, 1918.

11. Ringer, A. I., and Lusk, Graham: *J. Biol. Chem.* **7**:20, 1909-1910.

12. Ringer, A. I.: *J. Biol. Chem.* **15**:145, 1913.

13. Kocher, R. A.: *J. Biol. Chem.* **25**:571, 1916.

The question arises as to the nature of this protein sparing action of carbohydrates. It is held by some to be simply a matter of substituting sugar for protein as a source of energy, thus lessening katabolism. Landergren¹⁴ offered the further suggestion that carbohydrate ingestion relieved the body protein of the duty of maintaining a constant blood sugar level. As pointed out by Sherman, this would not explain an actual storage of nitrogen on an exclusive carbohydrate diet. It is believed by many able investigators that carbohydrate spares the protein of the body by inhibiting the intracellular ferments which tend to break down the cell protein—a true *sparing at the source*.

Janney,¹⁵ Sherman, Kocher and many others ascribe a more or less active rôle to the ingested sugar; that is, an aminization of lactic and pyruvic acids with the end-products of protein katabolism, and an actual construction of new tissue protein.

We consider that the evidence which we present in this communication definitely supports the last theory. Here we know that there is an extensive liver necrosis and we can follow the daily elimination of the nitrogen waste. On the addition of sugar to the diet the nitrogen excretion is markedly diminished, and concurrently liver repair takes place. The repair following sugar feeding is quite striking compared with that occurring in fasting. Moreover, the daily nitrogen elimination after the first great rise due to dead liver protein, can be further reduced by sugar administration; here again there is a consequent liver repair.

It is not possible to say from what source the protein split products are obtained which are combined with the sugar to form liver cell protein. There are at least two probable sources: (1) the necrotic liver cells; (2) the products of normal or accelerated cell katabolism in the body elsewhere than in the liver. One naturally thinks of the necrotic and autolyzing liver cells as a most probable source of nitrogenous split products, yet we believe the evidence does not altogether support this assumption. The rise of urinary nitrogen is greatest on the first three days following the chloroform anesthesia whether sugar is given or not. Moreover, during this period the liver cells show considerable autolysis, and we may imagine that much of the cell protein is split up, digested and removed, perhaps to account for much of the increased urinary nitrogen. The actual liver cell construction is most active from the third day on, when presumably the mass of

14. Landergren: Skand. Arch. f. Physiol. **14**:112, 1903. Abstr. Exp. Sta. Rec. **14**:1099. Cited by Sherman, Footnote 10.

• 15. Janney, N. W.: J. Biol. Chem. **20**:321, 1915; *ibid.* **22**:203, 1915; **23**:77, 1915; **24**:30 (Proc.) 1916.

necrotic liver cells is much less in evidence or almost completely removed. We are willing to admit that some of the protein split products from these liver cells may be stored in the body and used later to combine with the carbohydrate to form the new liver cells; but it seems more probable that the protein split products used to form new liver cells may be derived from the usual protein split products formed in the daily cell katabolism.

We are not prepared to explain the sustained high curve of nitrogen excretion which may persist (Chart 1) for many days following a chloroform injury combined with fasting. We may safely assume that most of the necrotic cell protoplasm has been removed in the first three or four days after the anesthesia, but the rapid wasting and great loss of nitrogen continues. One interesting possibility is to be considered — that the livers are so injured in such cases that the minimal amount of protein split product conservation is not kept up — conservation which goes on to a degree even in starvation. This suggestion would attribute a very important rôle to the liver — that of combining the sugar and protein split products into some form which can be used elsewhere in the body to rebuild its needed cells. There are observations in cases of acute yellow atrophy which may be harmonized with this suggestion.

SUMMARY

The curve of urinary nitrogen excretion of a dog makes a sudden rise after chloroform injury. The actual amount of nitrogen eliminated following injury is greater in a fasting than in a sugar fed animal. Furthermore, the curve of excretion often remains well above the starvation metabolism base line if fasting is continued after chloroform anesthesia. If sugar is given the curve immediately falls even below the pre-anesthetic base line.

Liver repair is much more rapid and complete on a sugar, or high carbohydrate diet than it is on starvation. In fact, an injury of one-half of each liver lobule may be completely repaired in nine days on a sugar diet, but only 50 per cent. repaired under fasting conditions.

This is convincing evidence that the "protein sparing action of carbohydrate" in this instance is a true *conservation of protein split products*. This evidence can not be explained as protein sparing at the source or as simple inhibition of protein autolysis or katabolism.

It is suggested that the liver may be the place in which this union of carbohydrate and protein split products may be made permanent, whether the resultant products are to be used in the liver or elsewhere in the body.

LIVER REGENERATION FOLLOWING CHLOROFORM INJURY AS INFLUENCED BY VARIOUS DIETS

MECHANISM OF PROTEIN SPARING ACTION OF FAT *

PAPER IV

N. C. DAVIS AND G. H. WHIPPLE, M.D.

SAN FRANCISCO

This article cannot be looked on as complete in any sense, yet the data have considerable value in conjunction with the experiments given in the other papers of the series. It is evident that more experiments are needed to determine the exact influence of the cooked parenchymatous organs and organ extracts on liver cell repair. Incomplete proteins, for example, gelatin, should be tested to ascertain if possible what repair can take place on such diets. The lipoids and allied substances may have a part in this reaction and the influence of thyroid and other ductless glands or extractives of these glands should be worked out. Some of this work we hope to carry out in the near future.

From the experiments at hand it is clear that the liver will regenerate at maximum speed following a unit chloroform necrosis if the animal is fed a diet rich in carbohydrate, a bread and milk diet or an ordinary mixed diet. The diets which rank next to this optimum group may be the parenchymatous organs (liver and kidney) and meat, perhaps brain, although this last diet is usually distasteful to dogs. Liver regeneration is rapid on these rich protein diets and more data may show that the optimum regeneration may at times follow the administration of such foods.

Thyroid fed in large amounts is known to favor tissue katabolism, but this does not favor liver regeneration and may even inhibit it. Under such circumstances the liver cannot take advantage of the protein split products and conserve them for use in construction of liver cells. It will be of considerable interest to observe the effect of large doses of thyroid combined with carbohydrate and of small doses of thyroid with and without carbohydrate.

Fat feeding supplies the most interesting observation brought out in this paper. Sufficient data are presented to show that liver injury will be regenerated just as rapidly as during complete fasting on a pure fat diet. In other words, the fat does not contribute in the least

* From the George Williams Hooper Foundation for Medical Research, University of California Medical School.

to the tissue building in the liver. We may make several deductions from this evidence when we recall that pure sugar makes possible a rapid and complete liver repair. Both fat and sugar are burned as fuel in the body and are recognized as "sparing protein" in one way or another. We have suggested in the preceding paper that sugar must "spare protein" by conservation of protein split products which are constructed into liver protoplasm. It is of course possible and even probable that sugar also is capable of "sparing protein" by acting at the source of protein katabolism and preventing this autolysis or tissue break down. Fat obviously acts as a "protein sparer" not by conservation of end-products and reconstruction of new liver tissue, but by some protecting action at the source of tissue katabolism.

These experiments mark out a clean-cut difference in the metabolism of fat and carbohydrate relating to protein construction and destruction. It may be that this reaction is limited to the peculiar conditions of these experiments, but we believe it may be applicable to general body metabolism. Surely the metabolism and cell repair of a large and important organ like the liver must play an important part in the body metabolism and give more than a hint concerning the reaction of other less rapidly functioning cells.

The striking difference between the fat feeding and brain feeding experiments is worthy of further study. It will be of some interest to determine in what way the neutral fats differ from brain extractives (cholesterol, lipins, etc.) when given in diets to influence liver repair.

The values of various foods and combinations of foods for promoting growth and maintaining weight and bodily activities have been extensively studied by Osborne and Mendel,¹ McCollum,² and a host of others. Such studies may have a bearing on our particular problem, although we have used comparatively short feeding periods. The effect of various diets on the growth of tumors has been enthusiastically studied by many investigators³ because of the tremendous practical value of such knowledge.

Hunt,⁴ Janney,⁵ Kendall⁶ and others have suggested that the thyroid has a rôle in regulating the supply of food for the formation

1. Osborne, T. B., and Mendel, L. B.: Feeding Experiments with Isolated Food Substances, Pub. Carnegie Inst., Washington, D. C., 1911; Pub. 156, Part II, *J. Biol. Chem.* **15**:311, 1913; **16**:423, 1913-1914; **20**:351, 1915.

2. McCollum, E. V.: Summarized in: *The Newer Knowledge of Nutrition*, The Macmillan Company, New York, 1918.

3. Sweet, J. E., Carson-White, E. P., and Saxon, G. J.: *J. Biol. Chem.* **15**:181, 1913. Van Alstyne, E., and Beebe, S. P.: *J. M. Res.* **29**:217, 1913-1914. Rous, Peyton: *J. Exper. M.* **20**:433, 1914. Robertson, T. B., and Burnett, T. C.: *J. Exper. M.* **23**:631, 1916.

4. Hunt, Reid: *Hygienic Lab. Bull.*, No. 69, 1910.

5. Janney, N. W.: *J. Biol. Chem.* **24**: 1916, Proc. 30.

6. Kendall, A. C.: *J. A. M. A.* **71**:871, 1918.

of living protoplasm. That other ductless glands have a function in governing growth and development is well recognized; Robertson⁷ has recently emphasized the action of the pituitary gland in this respect. We cannot deny that the activities of the organs of internal secretion may play an important part in cell regeneration and in liver repair.

MacCallum,⁸ Pearce,⁹ Whipple and Sperry¹⁰ have studied regenerative changes in the liver after necrosis, but without especial reference to the influence of diet.

Blood serum protein regeneration has been recently studied by Kerr, Hurwitz and Whipple.¹¹ It was clear that fasting delayed the serum protein regeneration and a heavy protein diet was most favorable for rapid repair. Under optimum conditions after a severe plasma depletion to about 30 or 40 per cent. of normal, the serum protein regeneration required from five to eight days. This slow curve of repair is very like the curve of regeneration noted in liver injuries. It suggests that the serum protein is built up with the same difficulty as the liver protein. The experiments indicate, further, that liver cells may be concerned in serum protein regeneration as a liver injury interferes with the serum protein repair.

METHODS

The chloroform injury has been quite definitely ascertained in each case here reported, usually by operative removal of a small piece of liver for microscopic examination on the second day following anesthesia.

Fluids such as cottonseed oil and suspension of thyroid powder were given by stomach tube; solid foods were left in the cages for consumption. Amounts are indicated in the individual protocols.

Repair has been determined microscopically at the end of a week or more, either by means of another operation or after sacrifice of the animal.

The technic of our experiments has been more fully explained in the other papers of this series. All operative procedures without exception were carried out under ether anesthesia.

EXPERIMENTAL OBSERVATIONS

All observations are given in the form of tables to facilitate a survey of the various groups of experiments. In addition, each experiment is given in the form of a history, including the necessary experimental details, histologic data and necropsy findings. These histories usually follow the proper tables.

7. Robertson, T. B.: *J. Biol. Chem.* **24**:363, 385 and 397, 1916.

8. MacCallum, W. G.: *Johns Hopkins Hosp. Rep.* **10**:375, 1902; *ibid.* *J. A. M. A.* **43**:649, 1904.

9. Pearce, R. M.: *J. M. Res.* **15**:99, 1906.

10. Whipple, G. H., and Sperry, J. A.: *Bull. Johns Hopkins Hosp.* **20**:1, 1909.

11. Kerr, W. J., Hurwitz, S. H., and Whipple, G. H.: *Am. J. Physiol.* **47**:356, 370 and 379, 1918.

TABLE 12.—LIVER REGENERATION ON BREAD AND SKIM MILK DIET

Experiment	Chloroform Hours	Liver Injury	Regeneration Diet	Liver Repair	Remarks
90 (Pup 2a)	1	1/3 necrosis; extensive, diffuse fat	Sacrifice in 2 days (control)	Milk and mixed diet; no preliminary starvation; Wt., 1.94 lbs.
(Pup 2b)	1	Estimated the same as 2a	Bread and skim milk ad lib. for 7 days	8th day: complete repair; no fat; much glycogen	Same diet as 2a; same age; Wt., 1.75 lbs.; sacrificed on 8th day
91 (Dog 18-82)	1½	1/2 to 3/5 necrosis; fat light over 2/5	2d day: bread and skim milk ad lib.	9th day: repair practically complete; trace of fat; much glycogen	Operation on 2d day after chloroform; feeding begun on 3d day; sacrificed on 9th day

EXPERIMENT 90.—*Regeneration on Bread and Skim Milk Diet.*—Pup 2a (control), a black female.

April 23: Pup is 6 weeks old; in good health; wt., 1.94 lbs.; previous milk and mixed diet. *Chloroform anesthesia for one hour* (from 10:55 to 11:55 a. m.).

April 24: Active; no food.

April 25: Sacrificed at 3:30; blood urea, 30 mg.; urea N, 14 mg.

Necropsy Report.—Blood clots slowly; clots are flabby. *Liver:* weight, 38 gm. Lobule centers are hard to discern; about two thirds of each lobule is opaque and white; outer zones of lobules are translucent gray. Intestine contains two round worms and several tape worms.

Microscopic Report.—*Liver:* Necrosis of about one third; extensive, diffuse fat deposits, especially toward lobule centers.

Pup 2b, a tan male.

April 23: Same litter as 2a, and on same diet; wt., 1.75 lbs. *Chloroform anesthesia for one hour* (from 10:55 to 11:55 a. m.); *bread and skim milk diet.*

April 24 to 30: Bread and milk *ad lib.*; eats well; noisy.

May 1: Wt., 1.38 lbs. *Sacrificed* at 10:30 a. m.; blood urea, 30 mg.; urea N, 14 mg.

Necropsy Report.—Blood clots quickly; viscera a little pale. *Liver:* weight, 54 gm.; no evidence of necrosis or fat.

Microscopic Report.—No necrosis or collapse in lobules; no fat; much glycogen; cells around central veins have a dense formation, and stain differently from the peripheries—possibly newly formed tissue.

EXPERIMENT 91.—*Regeneration on Bread and Skim Milk Diet.*—Dog 18-82, a young white female bull.

June 11: Wt., 18.63 lbs. *Chloroform anesthesia for one and a half hours*, with carbonate solution intravenously at the same time.

June 12: Wt., 18.63 lbs. Very lively.

June 13: Wt., 17.56 lbs. *Removed piece of liver* at 2 o'clock. Liver lobules show central necrosis involving from one half to three fifths of all cells. The remaining cells contain much fat. Lost considerable blood; gave epinephrin subcutaneously.

June 14: Wt., 17.2 lbs. Dog is rather weak; feeding begun; bread and skim milk *ad lib.*

June 15: Wt., 17.63 lbs.; June 16, wt., 18.06 lbs.; June 17, wt., 18.38 lbs.; June 18, wt., 18.38 lbs.

June 19: Wt., 18.25 lbs. *Bread and skim milk ad lib.*; dog is very active again.

June 20: Sacrificed at 9 a. m.; blood urea, 38 mg.; urea N, 17.7 mg.

Necropsy Report.—Liver: weight, 286 gm.; necrotic material and fat practically gone, but lobule centers are very prominent. *Spleen:* surface is quite nodular; malpighian bodies are very large and milky. *Kidney* cortex seems to have an unusual streaking with white.

Microscopic Report.—Liver: some lobule centers seem to have a very slight amount of stroma not filled out; a trace of fat, a few wandering cells, and much glycogen present.

The foregoing experiments show an excellent regeneration on bread and skim milk. This diet is rich in carbohydrate, but contains more protein than the sugar and potato diet fed in Experiment 88 (Paper III of this series). Both of these diets are very poor in fat. These mixed diets are, perhaps, somewhat better than pure carbohydrate for liver cell regeneration.

TABLE 13.—LIVER REGENERATION ON FAT DIETS

Experiment	Chloroform Hours	Liver Injury	Regeneration Diet	Liver Repair	Remarks
92 (Dog 19-5)	1½	2d day: 1/4 to 1/3 necrosis; severe cytoplasmic injury up to 1/2; fat throughout	Fat diet: butter, lard, fat meat, cottonseed oil	7th day: 1/5 to 1/4 not repaired; fat over 2/5	Operation on 2d day; operation on 7th day
93 (Dog 19-6)	1½	2d day: 1/4 to 1/3 necrosis; severe cytoplasmic injury up to 1/2; fat throughout	Fat diet: butter, lard, fat meat, cottonseed oil	7th day: 1/5 to 1/4 not repaired; slight scattering of fat	Operation on 2d day; operation on 7th day; almost the same picture throughout as in Exper. 92
94 (Dog 18-124)	1¼	2d day: 1/2 necrosis; some surrounding injury; 1/3 fatty	Fat diet: fat meat, lard, cottonseed oil; fat from beef hearts	7th day: 1/4 not repaired; 3/4 fatty	Operation on 2d day; operation on 7th day
95 (Dog 19-27)	1¼	2d day: about 3/5 necrosis; some fat throughout	Mixed food (control)	Operation on 2d day to find the necrosis obtained under these "standard" conditions
96 (Dog 19-27)	1¼	Estimated 3/5 as in Exper. 95	75 c.c. cottonseed oil daily	7th day: 1/4 to 1/3 not repaired; 3/5 fatty	Metabolism experiment; N rose about 75%, but fell below the pre-anesthetic base line by the 6th day; died under anesthetic on 7th day

EXPERIMENT 92.—*Regeneration on Fat Diet.*—Dog 19-5, an adult male Airdale.

July 17: Wt., 26.75 lbs. *Chloroform* anesthesia for one and a half hours with carbonate solution intravenously; previous starvation of three days.

July 18: Wt., 26.25 lbs. Apparently as well as usual; *butter and lard*.

July 19: Wt., 26.13 lbs. Vomited about 2 o'clock. *Piece of liver removed* at 2:45 p. m.; severe injury of one half, with actual necrosis involving from one fourth to one third of lobule; fat throughout; fat left in cage.

July 20: Wt., 26.2 lbs. Wound in good condition; eats fat all right

July 21: Wt., 25.94 lbs. Wound in good condition; fat diet *ad lib*.

July 22: Wt., 26.3 lbs. Losing appetite; added scraps of fat meat, and gave 100 c.c. cottonseed oil by stomach tube.

July 23: Wt., 25.9 lbs. Wound is opening; fat and oil as yesterday.

July 24: Wt., 25.56 lbs. Beginning distemper. *Piece of liver removed at 3 o'clock. Sections show scattered fat over central two fifths of lobules; central collapse of one fifth to one fourth (actual necrosis not repaired).*

July 25: Mixed diet.

EXPERIMENT 93.—*Regeneration on Fat Diet.*—Dog 19-6, a yellow adult male mongrel.

Aug. 19: Wt., 26.75 lbs. *Chloroform anesthesia for one and a half hours (from 9:10 to 10:40 a. m.); carbonate solution intravenously during anesthesia; previous starvation of three days.*

Aug. 20: Wt., 25.9 lbs. Quieter than usual; diet of *butter, lard* and a little cracker meal.

Aug. 21: Wt., 25.2 lbs. Eats *fat* well; bright and active. *Piece of liver removed at 1:15 p. m. Sections show necrosis of one fourth to one third, severe cytoplasmic injury up to one half, and scattering of fat to lobule peripheries.*

Aug. 22: Wt., 25.7 lbs. In addition to *fat mixture ad lib.*, gave 100 c.c. *cottonseed oil* by stomach tube.

Aug. 23: Wt., 26 lbs. Eats some *butter, lard* and *fat meat scraps*; 100 c.c. *cottonseed oil* by stomach tube.

Aug. 24: Wt., 26.2 lbs.; 100 c.c. *cottonseed oil*, and *fat scraps*.

Aug. 25: Wt., 26.3 lbs.; 100 c.c. *cottonseed oil*, and $\frac{1}{4}$ pound *butter*.

Aug. 26: Wt., 26.13 lbs. *Fat scraps ad lib. Piece of liver removed at 3 o'clock. Sections show a moderate central collapse, distinctly greater than after regeneration on meat diet (experiment 99); wandering cells present; slight scattering of fat.*

EXPERIMENT 94.—*Regeneration on Fat Diet.*—Dog 18-124, a young, black and white female.

Oct. 11: Wt., 13.75 lbs. Isolated for starvation before daily feeding, active; previously fed thyroid, chloroformed, and regenerated on carbohydrate diet.

Oct. 12: Wt., 13.44 lbs.; Oct. 13, wt., 13.25 lbs.; *starvation*.

Oct. 14: Wt., 13 lbs. In good condition; fourth day of starvation. *Chloroform anesthesia for one and a quarter hours (from 2 to 3:15 p. m.).*

Oct. 15: Wt., 12.44 lbs. Bright and active; 75 c.c. *cottonseed oil* by stomach tube; also *fat meat* left in cage.

Oct. 16: Wt., 12.38 lbs.; 75 c.c. *cottonseed oil; fat scraps and lard. Piece of liver removed at 3:30 p. m. Sections show one half necrosis; fat involves over one third and is moderate in amount; some vacuolated injured cells surrounding necrosis.*

Oct. 17: Wt., 12.38 lbs. Bright and active; 75 c.c. *cottonseed oil*, also *fat scraps*; vomited some; *fat* from beef hearts in p. m.

Oct. 18: Wt., 12.63 lbs.; 75 c.c. *cottonseed oil* and *fat* from beef hearts; vomits a little.

Oct. 19: Wt., 12.13 lbs. Active as usual; wound red and swollen; food as yesterday.

Oct. 20: Wt., 12.44 lbs. Active; wound slightly open; 75 c.c. *cottonseed oil, lard*, and *fat* from beef hearts.

Oct. 21: Wt., 12.38 lbs. *Fat only. Piece of liver removed at 1:30 p. m. Sections show liver lobules one fourth unrepaired; the remaining liver cells show fatty degeneration.*

EXPERIMENT 95.—*Simple Starvation and Chloroform (Control).*—Dog 19-37, a yellowish-brown male mongrel.

Oct. 2: Wt., 33.5 lbs. Isolated for starvation before daily feeding; healthy and very active.

Oct. 3: Wt., 32.25 lbs.; Oct. 4, wt., 31.7 lbs.; *no food*.

Oct. 5: Wt., 31.75 lbs. *Chloroform for one and one-fourth hours (from 9:25 to 10:40 a. m.).*

Oct. 6: Wt., 30.75 lbs. Quiet.

Oct. 7: Wt., 30.2 lbs. Quiet but fairly bright. *Piece of liver removed at 3 p. m.* Sections show hyaline necrosis involving about three fifths of each liver lobule; some fat to lobule peripheries. Mixed food.

EXPERIMENT 96.—*Liver Regeneration on Cottonseed Oil.*—Dog 19-37, a yellowish-brown male mongrel.

Date	Weight, Lbs.	Urine		Nitro- gen, Gm.	Diet	Remarks
		Cath., C.c.	Cage, C.c.			
Oct. 28	32.94	Water ad lib.	Dog normal
29	31.5	Bladder washed	250 c.c. water	
30	31.25	22	340	4.25	250 c.c. water	
31	30.56	6	310	4.12	75 c.c. oil; 150 c.c. water	Vomited; Kjeldahl shows no N in vegetable oil
Nov. 1	29.38	22	440	6.10	Chloroform anesthesia for 1½ hours (2:30-3:45 p. m.) 75 c.c. oil; 150 c.c. water	Feces
2	28.9	12	300	7.35	a. m. 75 c.c. oil; 150 c.c. water p. m. 75 c.c. oil; 150 c.c. water	Vomited in a. m.
3	28.5	..	440	6.02	75 c.c. oil; 350 c.c. water	Feces
4	28.5	14	225	5.62	75 c.c. oil; 350 c.c. water	Feces
5	28.25	1	230	4.36	75 c.c. oil; 350 c.c. water	Feces
6	27.75	20	150	3.55	75 cc. oil; 350 c.c. water	
7	28.2	5	330	3.89	Died under anesthesia

Necropsy Report.—Greatly distended heart and congested viscera. *Liver* is quite distinctly dimpled, and lobule centers are red, giving the impression of unrepaired injury.

Microscopic Report.—*Liver*: about one fourth to one third of each lobule unrepaired; marked capillary stasis; fatty degeneration involves over three fifths of the liver cells. *Kidneys*: a little pyelonephritis.

The experiments listed in Table 13 indicate that the liver repair on a fat diet is very little better than that on starvation. Experiment 96, in which the daily output of nitrogen was determined, shows that the cottonseed oil has a definite sparing action on protein. The fact that repair was very incomplete in this case, and that there was an enormous output of nitrogen immediately following chloroform anesthesia, indicates that the oil did not actively "fix" much of the necrotic liver split products for new protoplasm, but exerted its influence more actively on sparing of bodily katabolism after the liver waste was removed. These phenomena are, therefore, capable of explanation on dynamic grounds alone. We must not forget, however, that a relatively small part of the oil molecule—the glycerol radical—can be made available as sugar in the body, and might play a more or less insignificant part in tissue building. Mendel and Lewis¹² found a delay of nitrogen elimination following ingestion of cottonseed oil. Classical metabolism experiments which may be found cited by Lusk,¹³ Sherman,¹⁴

12. Mendel, L. B., and Lewis, R. C.: J. Biol. Chem. **16**:37, 1913-1914.

13. Lusk, Graham: The Elements of the Science of Nutrition, Ed. 3, W. B. Saunders and Company, 1917.

14. Sherman, H. C.: Chemistry of Food and Nutrition, Ed. 2, The Macmillan Company, 1918.

and in books on nutrition by other authors, prove that carbohydrate cannot be wholly replaced by fat as a protein sparer, when the subject is in nitrogen equilibrium.

TABLE 14.—LIVER REGENERATION ON DIETS OF LIVER, KIDNEY, MUSCLE, BEEF EXTRACT, BRAIN, AND POWDERED THYROID

Experiment	Chloroform Hours	Liver Injury	Regeneration Diet	Liver Repair	Remarks
97 (Pup 19-45)	1	2d day: 1/2 to 3/5 necrosis; moderate fat over 2/5	Ground liver	7th day: repair good; lack of regeneration not exceeding 1/5; trace of fat	Operation on 2d day; sacrifice on 7th day
98 (Pup 19-56)	1	2d day: slight necrosis; vacuolated cells and fat over 1/2	Ground kidney	7th day: normal	Operation on 2d day; operation on 7th day
99 (Dog 19-6)	1½	2d day: 1/4 to 1/3 necrosis; cytoplasmic injury up to 1/2; very little fat	Skeletal muscle	7th day: slight lack of repair; trace of fat	Operation on 2d day; operation on 7th day; repair better than Exper. 93
100 (Dog 19-28)	1½	2d day: 2/5 necrosis; moderate fat over 2/3	Skeletal muscle	9th day: about 1/4 not repaired; trace of fat; glycogen +	Operation on 2d day; operation on 9th day
101 (Dog 19-74)	1½	2d day: 1/2 necrosis; moderate fat over 1/3	Beef extract, 10 gm. daily	9th day: 1/3 not repaired; moderate fat over 1/3	Operation on 2d day; operation on 9th day
102 (Dog 19-92)	1	2d day: 2/5 to 1/2 necrosis; moderate fat over 1/3	Brain	7th day: 1/4 not repaired; trace of fat	Operation on 2d day; operation on 7th day
103 (Dog 19-39)	1½	Estimated 1/2 to 3/5 necrosis; see Exper. 82	Thyroid powder, 3 gm. daily	7th day: 1/3 not repaired; fat in large globules over 2/5	Operation on 7th day

EXPERIMENT 97.—*Regeneration on Liver Diet.*—Dog 19-45, a black mongrel, female pup.

Oct. 8: *Chloroform anesthesia for one hour*; has been fed a diet of alfalfa meal and cracker meal.

Oct. 9: Wt., 8.38 lbs. *Ground liver*, 150 gm.; active; not clinically sick.

Oct. 10: Wt., 8.5 lbs. *Ground liver*, 150 gm. *Piece of liver removed* at 1:45 p. m. Sections show necrosis involving one half or three fifths of each liver lobule, and fatty degeneration of moderate degree involving the remaining cells.

Oct. 11: Wt., 8.44 lbs.; Oct. 12, wt., 8.25 lbs.; Oct. 13, wt., 8.3 lbs.; *ground liver*, 160 gm., daily.

Oct. 14: Wt., 8.25 lbs. *Ground liver*, 140 gm.; wound opening a little.

Oct. 15: Wt., 8.25 lbs. Sacrificed in a. m.

Necropsy Report.—Small walled-off abscess beneath abdominal incision. *Liver*: finely dimpled; normal color; necrosis and fat not apparent. *Kidneys*: left shows a couple of small yellowish-white blotches in cortex suggesting abscesses; other viscera negative.

Microscopic Report.—*Liver*: repair is good in most places; some areas show lobules not completely regenerated (lack of repair probably not exceeding one fifth). *Kidneys*: a few abscesses at juncture of cortex and medulla.

EXPERIMENT 98.—*Regeneration on Kidney Diet.*—Pup 19-56, a female colic pup.

Oct. 16: Wt., 6.63 lbs. *Chloroform anesthesia for one hour* (from 10:30 to 11:30 a. m.); beef extract for four days previously; kidney, 150 gm., at 4:30 p. m.

Oct. 17: Wt., 6.75 lbs. A little dull; kidney, 150 gm.

Oct. 18: Wt., 6.8 lbs. Kidney, 150 gm. *Piece of liver removed* at 3 p. m. Sections show a minimal injury; very little necrosis, but a cytoplasmic disturbance, with vacuolization and deposition of fat over one half of each lobule; dog almost died under anesthesia.

Oct. 19: Wt., 6.8 lbs.; Oct. 20, wt., 6.75 lbs.; Oct. 21, wt., 6.9 lbs.; kidney, 150 gm. daily; continues bright and active.

Oct. 22: Wt., 6.8 lbs. No food.

Oct. 23: Wt., 6.63 lbs. Kidney, 200 gm., early in morning. *Piece of liver removed* at 3 p. m. Sections show a practically normal liver.

Oct. 24: Pup is up and active; experiment discontinued. Mixed food.

EXPERIMENT 99.—*Regeneration on Lean Meat Diet.*—Dog 19-6, a yellow, adult male mongrel.

July 20: Wt., 28.25 lbs. *Chloroform anesthesia for one and a half hours* (from 9:15 to 10:45 a. m.); saline intravenously during first hour of anesthesia; starvation for three days previous to chloroform.

July 21: Wt., 26.94 lbs. Very active; lean meat diet.

July 22: Wt., 27.13 lbs. *Lean meat diet ad lib.* *Piece of liver removed* at 11 a. m. Sections show very little fat; actual necrosis of one fourth to one third, with severe cytoplasmic reaction up to one half (cells swollen, little cytoplasm).

July 23: Wt., 28.06 lbs. Very active; wound in good condition; eats meat *ad lib.*

July 24: Wt., 27.63 lbs.; July 25, wt., 27.7 lbs.; July 26, wt., 27.44 lbs.; skeletal muscle *ad lib.*

July 27: Wt., 27.44 lbs. Operative wound slightly open. *Piece of liver removed* at 10 a. m. Sections show a slight amount of unrepaired injury with central collapse; some vacuolated cells in region of lobule centers; a few fat droplets.

EXPERIMENT 100.—*Regeneration on Lean Meat.*—Dog 19-28, a fox terrier, male adult.

Dec. 21: Wt., 15.8 lbs. Bright and healthy. *Chloroform anesthesia for one and a quarter hours* (from 11:15 to 12:30); casein digest by stomach tube a few minutes before anesthesia; skeletal muscle *ad lib.* in the evening.

Dec. 22: Wt., 16.2 lbs. *Lean meat ad lib.*; eats well; clinically not sick.

Dec. 23: Wt., 16 lbs. Appears quite well; meat diet. *Piece of liver removed* at 2:30 p. m. Sections show hyaline necrosis involving two fifths of each lobule and moderate fatty degeneration involving the remaining liver cells.

Dec. 24: Wt., 15.13 lbs. A little dull after operation.

Dec. 25 to 27: *Meat ad lib.*; eats well.

Dec. 28: Wt., 16.5 lbs. Operative site is swollen and red; chest and pelvic regions show purpuric areas; meat *ad lib.*; eats well.

Dec. 29: Wt., 16.13 lbs. Wound looks bad but is not open; meat as before.

Dec. 30: Wt., 16.44 lbs. Wound somewhat better; meat taken all right. *Piece of liver removed* at 1:30 p. m. Sections show a little fat and central collapse of perhaps one fourth; glycogen ++; experiment discontinued; mixed food.

EXPERIMENT 91.—*Regeneration on Beef Extract.*—Dog 19-74, a young, black and white male terrier.

Dec. 7: Wt., 11.8 lbs. *Chloroform anesthesia for one and a quarter hours*; fourth day of starvation.

Dec. 9: Wt., 11.06 lbs. Active. *Piece of liver removed* in p. m.; bled freely. Sections show necrosis involving one half of each liver lobule and a moderate degree of fatty degeneration involving about one third of the lobule.

Dec. 10: Wt., 10.94 lbs.; Dec. 11., wt., 10.7 lbs.; Dec. 12, wt., 10.5 lbs. *Beef extract*, 10 gm., + kaolin in 100 c.c. water, by stomach tube daily.

Dec. 13: Wt., 10.44 lbs. Wound opening superficially; *beef extract*, 10 gm., as before.

Dec. 14: Wt., 10.25 lbs.; Dec. 15, wt., 10 lbs.; weak and thin; *beef extract*, 10 gm., daily.

Dec. 16: Wt., 9.94 lbs. *Beef extract*, 10 gm., in a. m. *Piece of liver removed* at 2:15 p. m. Sections show a collapse and lack of repair involving the central one third of each liver lobule; there is moderate fatty degeneration involving one third of the lobule. Mixed food and recovery.

EXPERIMENT 102.—*Regeneration on Brain*.—Dog 19-92, an adult male terrier.

Dec. 25: Isolated for starvation; active.

Dec. 26 to 27: Fasting.

Dec. 28: Wt., 18.63 lbs. Somewhat thin, but active. *Chloroform anesthesia* for one hour (from 11 to 12); *brain*, 200 gm. in p. m.

Dec. 29: Wt., 18.63 lbs. Active; *brain*, 200 gm.

Dec. 30: Wt., 17.9 lbs. Weak. *Piece of liver removed* at 3:45 p. m. Sections show hyaline necrosis involving from two fifths to one half of each liver lobule, and fatty degeneration involving the midzone (one third in amount); ate 300 gm. *brain* late in evening.

Dec. 31: Wt., 17.9 lbs. Sick; *brain*, 200 gm., eaten.

Jan. 1, 1919: Wt., 17.38 lbs. Brighter than yesterday; ate 300 gm. *brain*.

Jan. 2: Wt., 17 lbs. *Brain ad lib.*; ate 330 gm.

Jan. 3: Wt., 16.5 lbs. *Brain ad lib.*; ate about 250 gm.

Jan. 4: Wt., 15.75 lbs. Mixed food. *Piece of liver removed* at 11:30 a. m. Sections show collapse and lack of repair involving the central one fourth of each liver lobule. There is a trace of fatty degeneration.

EXPERIMENT 103.—*Liver Regeneration on Thyroid Feeding*.—Dog 19-39, a female Airdale.

Date	Weight, Lbs.	Urine—		Nitro- gen, Gm.	Diet	Remarks
		Cath., C.e.	Cage, C.e.			
Nov. 23	27.38	Water ad lib.	Dog normal
24	26.25	Bladder washed	300 c.e. water	Feces ++
25	25.63	96	400	2.41	250 c.e. water	
26	25.06	2	375	2.06	300 c.e. water	
26	Chloroform anesthesia for 1½ hours				(10:00-11:15 a. m.)	
27	23.63	83	450	3.50	300 c.e. water; 3 gm. powdered thyroid	Feces +; thyroid contains 126 mg. N per gram
28	23.0	22	385	4.48	300 c.e. water; 3 gm. powdered thyroid	See control Exper. 82, same dog; 1/2 to 3/5 necrosis
29	22.56	18	355	3.86	300 c.e. water; 3 gm. powdered thyroid	
30	22.2	10	300	3.09	300 c.e. water; 3 gm. powdered thyroid	
Dec. 1	21.56	18	340	3.37	300 c.e. water; 3 gm. powdered thyroid	
2	21.38	4	290	3.68	300 c.e. water; 3 gm. powdered thyroid	
3	21.13	1	275	3.71	Water ad lib.	Metabolism discontinued; mixed food
3	Piece of liver removed at 3 p. m.; 1/3 unrepaid; fat over 2/5					

Experiment 97 shows a very good regeneration on liver diet and the initial injury was almost maximal. Experiment 98 shows complete repair on kidney diet, but in this case the initial injury was slight. Both of these experiments were on pups, and age may be a definite factor in repair.

Experiments 99 and 100, using skeletal muscle as reparative diet, indicate a good regeneration, although probably not as thorough as would have occurred with a high carbohydrate or a mixed diet intake (such as bread and skim milk).

Experiment 101 shows very imperfect repair on beef extract feeding, which would indicate that fairly liberal amounts of extractives alone are not conducive to active repair. It will be recalled (Paper I of this series) that beef extract gave very good protection against chloroform injury when fed before the anesthetic.

Brain diet (Experiment 102) seems to equal skeletal muscle in reparative efficiency and to be distinctly better than the fats. The striking difference between brain and fat diets deserves further investigation.

Thyroid feeding alone (Experiment 103, Dog 19-39) certainly does not stimulate liver repair. Reference to the nitrogen curve of this animal reveals a sustained high output during the experiment. This seems to indicate a stimulated katabolic activity, and probably a deleterious or destructive rather than a reparative action on the injured organ. The thyroid used was an Armour preparation, and had previously been shown by Dr. Rohde to increase greatly the nitrogen metabolism in normal animals in the dosage here employed.¹⁵

GENERAL DISCUSSION

It is clear from the experimental data given that liver regeneration can be completed more rapidly on a diet rich in carbohydrate than on a very rich protein diet. This applies to mixed diets like bread and skim milk as contrasted with lean meat diets. We wish to point out a decided difference in liver regeneration as compared with serum protein regeneration. Kerr, Hurwitz and Whipple¹¹ found that serum proteins, after a considerable depletion, were regenerated best on a rich protein diet, for example, meat. It is possible that the differences noted may be explained by inherent differences in the proteins which are being formed with unusual speed in the body. Certain foods may contain ingredients especially suited to construct a certain type of body protein but unsuited for another type of body protein. It is significant that the abundant mixed diet gives an optimum regeneration in such instances.

The difference in regenerative power between the parenchymatous organs and ordinary skeletal muscle here noted may be only apparent. Pups were regenerated on liver and kidney, while adults were fed the muscle; there is a possible difference due to age. On the other hand, liver may be better than muscle, because chemically more nearly the

15. Rohde, A.: *J. Biol. Chem.*, 1919. To be published.

equivalent of the tissue which is regenerated. We have shown (Paper I of this series) that the parenchymatous organs are more protective against chloroform injury than skeletal muscle when fed during the days preceding anesthesia.

Thyroid may accelerate synthesis when given in small amounts with foods, as Janney suggested, but in the experiment here presented it was given in large quantities with no food, and we observed the well known action of increased metabolism, with a continued high nitrogen output, and no increase in liver repair.

The lack of repair on a fat diet is certainly quite striking when compared to the results with carbohydrates, proteins and mixtures of the two. Fat under these experimental conditions has a very minor rôle in tissue building, and apparently is limited to its dynamic function as a fuel in protein sparing.

SUMMARY

A diet of bread and skim milk gives the optimum repair following a unit chloroform liver necrosis. A similar reaction is to be expected with any mixed diet rich in carbohydrate. A liver necrosis involving the central one-half of every lobule (50 per cent. of all liver parenchyma) will usually be completely repaired in from seven to nine days.

A diet of cooked skeletal muscle is not as favorable for rapid liver repair as the rich carbohydrate diet.

A diet of cooked liver or kidney is more favorable for rapid liver repair than a meat diet. This diet of parenchymatous organ tissue approximates the rich carbohydrate diet in efficiency of liver repair.

Beef extract given alone does not favor liver repair, which indicates that meat extractives are not particularly concerned in the reaction of liver repair.

Thyroid powder given in large doses with no food does not stimulate liver repair, but does accelerate tissue katabolism and increase nitrogen elimination. This accelerated katabolism may even impede the liver repair which is to be expected in starvation.

Brain feeding is favorable to liver regeneration and repair. This diet approximates lean meat feeding in its favorable influence on liver repair. In this respect the brain diet stands in marked contrast to the fat diets.

Fat diets (vegetable oils, butter, lard, beef fat, etc.) do not aid in liver regeneration. The same repair is to be observed during fasting control periods. The fat diet can spare the proteins of the animal at the source, but *cannot act in conservation of protein material* by taking an active part in reconstruction of new protein substance.

NONEPIDEMIC "EPIDEMIC" MENINGITIS *

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INTRODUCTION

Most textbooks define meningitis (in this paper the term "meningitis" will be used to denote only meningococcus meningitis) as "an infectious disease, occurring sporadically and in epidemics" The name "cerebrospinal fever" is now commonly found in the literature. But since "epidemic cerebrospinal fever" and "epidemic meningitis" are terms so firmly embedded in the professional as well as the lay mind, the epidemic character of this disease is emphasized out of all proportion to its sporadic manifestations.

Epidemics are concomitants of crowding. Both Osler¹ and Rosenau² emphasize crowding in association with meningitis. "The concentration of individuals, as of troops in large barracks, is a special factor; recruits and young soldiers are specially liable."¹ "Cerebrospinal fever is a disease of infants and soldiers. . . . Crowding and close personal contact favor the spread of the infection. . . . The disease prevails especially in the winter and spring, and is spread mainly by healthy 'carriers.' Crowding is the chief hygienic factor for its spread among troops."² Among soldiers, therefore, it is the epidemic and not the sporadic element that is emphasized.

In the treatment of meningitis, immune serum is considered by many a specific for the reduction of mortality. Havard,³ for example, says: "This serum has reduced the mortality from 73 to 25 per cent. in adults, and less than 20 per cent. in children." Flexner⁴ emphasizes the necessity of using a potent serum, the potency being estimated by titration, and insists that this serum be given early, in appreciable amounts, and at frequent intervals. Given these factors, he concludes (p. 27) from a considerable number of statistics, among them detailed studies in Texas and Louisiana, that the mortality may be reduced over 50 per cent. by the use of the serum.

* From the Base Laboratory, Hospital Center, Allery, Saone et Loire, France.

1. Osler: Principles and Practice of Medicine, 1918, p. 109.

2. Rosenau: Preventive Medicine and Hygiene, 1918, p. 1260.

3. Havard: Military Hygiene, 1917, p. 91.

4. Flexner: Mode of Infection, Means of Prevention and Specific Treatment of Epidemic Meningitis, Monograph, from the Rockefeller Institute for Medical Research, 1917, p. 15.

Number of Cases at Center

■ = Cases of Meningococcus Meningitis

▨ = Meningococcus Carriers

□ = Contacts Cultured.

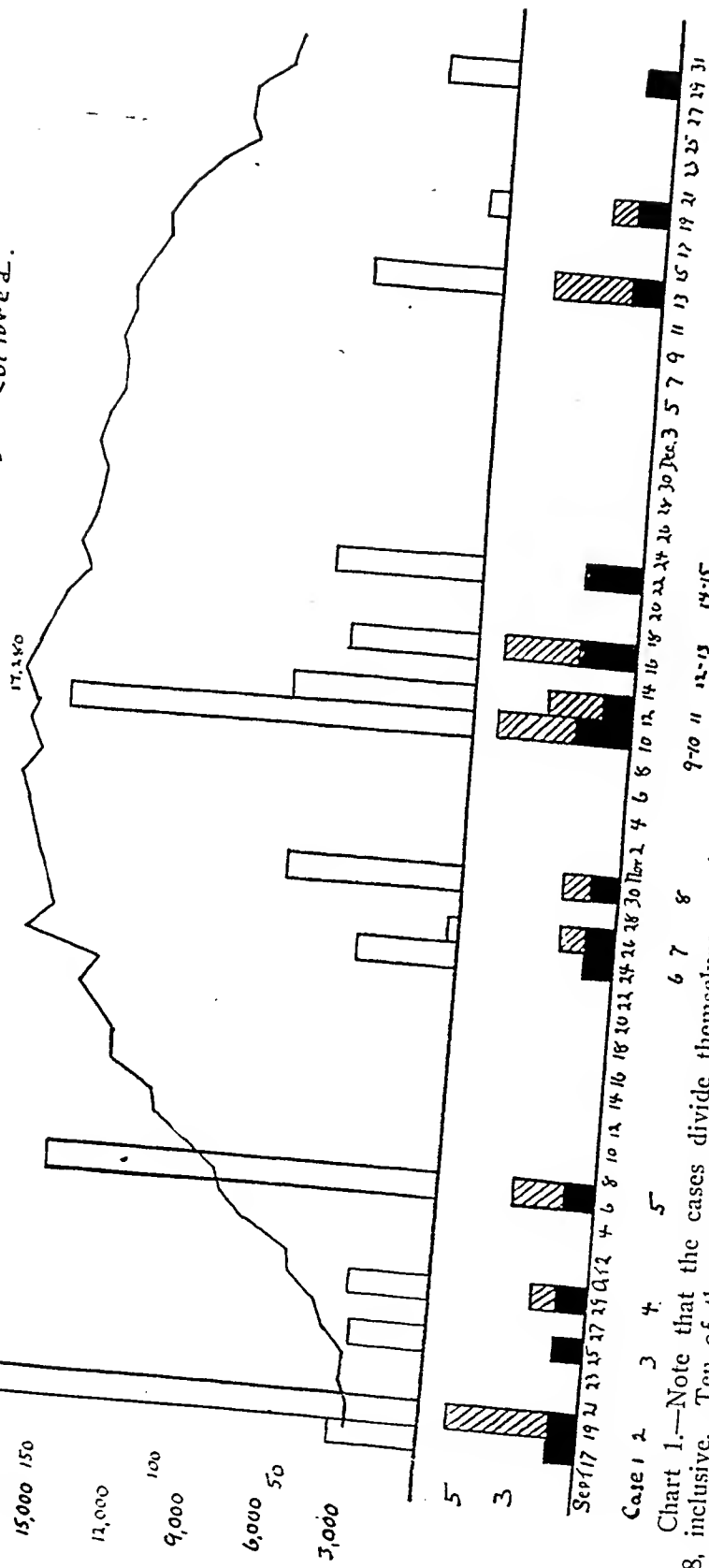


Chart 1.—Note that the cases divide themselves roughly into four groups, cases 1 to 5, 6 to 8, 9 to 15, and 16 to 18, inclusive. Ten of the carriers found when the largest number of patients were at the center. Note also that what is a common experience, that the immediate contacts are most likely to become carriers, since the immediate contacts were cultured in every case.

The series in this paper is studied with especial reference to the epidemic manifestations of meningitis and its amenability to treatment with serum.

EPIDEMIOLOGY

Up to Jan. 1, 1919, there had been eighteen cases of meningitis at this center. During this period of three months and a half there were 29,196 admissions and more than 2,000 personnel here, giving an incidence of meningitis of 0.56 per thousand. The first case occurred about Sept. 17, 1918. The exact date is not in our records, since this case was handled by one of the unit laboratories.

The first point to be considered is the introduction of the organism at this center. There were four cases in which the diagnosis was made within a very short time after their arrival here. The patient, Case 2 (Chart 1) had been sick on the transport and at Brest something over a week before arriving at camp. There was no meningitis on the boat and the trip across the Atlantic took sixteen days. The patient shared a stateroom with another officer previously reported as a meningitis carrier in the States. This carrier had been held for three negative cultures, and, according to his own story, had kept up a rather vigorous treatment with dichloramin-T even after release. However, his supply of dichloramin-T gave out on the boat and he was forced to desist from spraying. As soon as the diagnosis on Case 2 was made here, the unfortunate roommate was again quarantined as a possible carrier. Repeated nasopharyngeal cultures, however, did not confirm this. Cases 4 and 7 were diagnosed the fourth day after arrival, and Case 14 on the second day. The admission diagnosis in this last case was "influenza," but in the other two the admission diagnoses could not be ascertained. Twelve of the other cases were in the center from six days to four months previous to diagnosis. In two cases the length of time here could not be determined. It is probable, then, that four cases at least, Cases 2, 4, 7 and 14, were infected outside of the center and may be responsible for introducing a certain amount of the infection here.

The introduction of the infection by carriers must be considered. The only individual known to have been a meningitis carrier previously was not found to be one here. No cultures were taken before the occurrence of the first cases, and then only on contacts, so that all the carriers found may well have become infected from the cases. This theory is further borne out by the fact that no chronic carriers were discovered. By chronic carriers is commonly meant individuals who harbor the organism over a period of months and occasionally indefinitely. Some authors place the burden of infection on such carriers,

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Base Hospital 97				Evacuation Hospital 19				Base Hospital 56				Base Hospital 70				Base Hospital 49				Major Transport			
16				14				7				14				14				3			
18				11				8				17				4				3			
2 (Ent 22)				12				13				13				9				10			
Convalescent Camp				Base Hospital 56A				Engineer & Labor Section				Base Hospital 26				Base Hospital 15							
1				11				12				13				9							
2				6				13				13				10							
Road				Road				Road				Road				Road							

Chart 2.—Note that the cases appear apparently at random through the center, only two of the twelve sections having no case. Not more than three cases occurred in any one section. In the two sections Base Hospital 56 and Base Hospital 25, where the cases suggest association because of location and time, no such association could be established. Case 1 developed while Evacuation Hospital 22 occupied the section which was later taken over by Base Hospital 97.

claiming to find one or more among the contacts of each case. The most persistent carrier here cleared up in a little over a month. It is reasonable to assume, then, that carriers were infected by cases, rather than the reverse. There was no known case of meningitis in the immediate civil population.

Once the organism had been introduced, the spread from case to case directly or by carriers was investigated. The lack of any apparent relation between the various cases as they developed, was at once very striking, and is shown on Chart 2. This might almost be a chart of any noncontagious disease rather than of a disease spread by direct contact, in which case localized foci of infection are likely to appear. This lack of localized foci is even more surprising when the extreme crowding throughout the center is considered. The curve on Chart 1 shows the daily number of patients in the hospital. During the October and early November drive, the curve rose rapidly until at the signing of the armistice, November 11, it reached its height, with a total of 17,250 patients. Including a personnel of about 2,000, there were roughly 20,000 individuals at the center. Designed as a 10,000 bed center, crowding was unavoidable. Expansion tentage was slow in arriving, so that seventy beds were crowded into wards intended for fifty, with only a narrow space between every second bed. Red Cross huts and all available barracks were utilized. It would have been physically impossible to make use of the "spacing out" recommended by Glover,⁵ as a preventive of an epidemic of meningitis. Thus the stage was all set for an epidemic, and with the discovery of seven cases (Cases 9 to 15, inclusive) in an interval of twelve days, it was feared that it had actually begun. But aside from culturing contacts, in most cases only those immediately exposed, and isolating the positive carriers discovered, nothing was done, such as following the carrier index, wholesale masking, etc. Yet it was three weeks before the next case developed. Certainly meningitis here could not be termed "epidemic."

Association between cases was extremely rare, Cases 6 and 8 showing the closest of any. Case 6 developed in Base Hospital 56-A and was sent to the observation ward in Base Hospital 56, where the diagnosis of meningitis was made after a three-hours' stay. The patient was moved to the meningitis ward. Case 8 had already been in this ward for one day when Case 6 arrived, and was diagnosed meningitis five days later. In the observation ward all patients were kept in bed, all beds cubicled and all attendants masked. The effective-

5. Glover: "Spacing-Out" in Prevention of Military Epidemics of Cerebrospinal Fever, *Brit. M. J.* 2:509 (Nov. 9) 1918.

ness of the individual quarantine is suggested by the fact that when the ward was cultured on the day that Case 6 was diagnosed, no carriers were found. The two cases were on opposite sides of the aisle and three beds apart. There was no known direct contact. Cases 9 and 10, Base Hospital 25, occurring on the same day, were never together so far as is known, not having been in the same ward. The same was true of Cases 16 and 18 in Base Hospital 97, except that, instead of developing on the same day, there was an interval of sixteen days between them. Base Hospitals 56 and 49 had Cases 7 and 8, and 4 and 5, respectively, but with no demonstrable association. Though no authors attempt to state definitely the incubation period of meningitis, eighteen to eighty-three days, the interval elapsing between all other cases occurring in the same section, seems a considerable time to suggest a direct droplet infection between cases. Direct droplet infection from cases or carriers is commonly accepted as the mode of infection in this disease¹ (p. 4). That an individual may harbor the organism in his nasopharynx for an indefinite time until "prepared field," "lowered vitality," or "increased susceptibility," develops, before coming down with the disease, is theoretically possible. But it seems reasonable to assume that a person who is susceptible to meningitis is more likely to come down with the disease during the first few weeks that he is harboring the organism in his nasopharynx, than afterwards. This is borne out by the fact that it is so extremely rare for a known carrier to come down with meningitis.

An effort to demonstrate the relation between the cases was also made by determining the type of the meningococcus in each case. This is discussed more in detail under Bacteriology. The results, though not entirely satisfactory, show that the meningococci found were of two or more types.

With each new case a number of contacts were cultured, varying from 2 to 216. Chart 1 shows the number of contacts cultured and the number of carriers discovered. Of all, 2.1 per cent. were positive. As far as control was concerned, it made no difference whether a whole ward, a whole organization, or only the immediate bed mates were cultured. There was no evidence of a carrier spreading the disease from one case to another, neither did any known carrier come down with the disease. This was precisely the experience in Texas where, in the winter of 1917-1918, in the department laboratory, wholesale culturing of company streets, train loads of recruits and even larger units was abandoned and attention was confined to the immediate tentmates of the patients, with certainly no increase in the incidence of meningitis. So here, wholesale culturing was discarded and attention was focussed on those immediately exposed. But at

times our efforts at selective culturing met with some opposition from the clinicians. As with diphtheria,⁶ so with meningitis, the conclusions were that wholesale culturing gave a false sense of security, and consumed valuable time, materials, and effort, which might much better be used elsewhere so far as controlling the spread of meningitis was concerned.⁶

BACTERIOLOGY

It was early seen that the type of organism in each case would be of interest in its relation to epidemiology, since if two cases showed different types of meningococci in the spinal fluids, all possibility of cross infection would be ruled out at once. So, because of the striking isolation of practically every case from all others, it was felt that the organisms in many of the cases might well be of different types.

In order to type the meningococci in each case it was, of course, necessary to obtain a culture of the organism. For this purpose whole brain medium was used, prepared as follows:

Human brain, being available because of frequent necropsies (in the States, beef brain gave equally good results), was cut with a cork borer or potato punch, and a cylinder about 4 cm. long was put in each test tube. This was autoclaved for thirty minutes at from 12 to 15 pounds, and was ready for use. These tubes were sent out when a puncture was to be made, and 10 or 15 drops of spinal fluid were added directly at the bedside. Ward surgeons were urged not to "flood" the tubes. Another brain tube was planted with about 0.5 c.c. of spinal fluid as soon as the material reached the laboratory. Both tubes were put in the incubator at once to prevent chilling. However, the meningococcus seems to be less susceptible to variations of temperature than one is at times led to suppose. Frequently there was considerable delay in transmitting the specimens to the laboratory with no effort at keeping the material at body temperature, yet the organisms were not killed as shown by the abundant growth on the medium the next morning.

That the brain medium is of service in cases where the diagnosis was questionable, is well demonstrated in Case 10. The patient had been ailing for a week with vague symptoms before he was tapped. The fluid showed: "18 c.c. of clear, slightly greenish fluid, cell count 36 per c.mm., 60 per cent. dymorphonuclears; Nonne negative, albumin faintly positive; no organisms seen on smear; more suggestive of tuberculous meningitis than of meningococcus meningitis, though the findings are not conclusive." The next morning, smear from the brain medium showed abundant gram-negative diplococci which proved to be meningococci on agglutination. That it is an excellent medium for keeping meningococcus stocks is shown by the fact that after ten weeks without transplantation cultures were still alive. This

6. Meyer, Voltmann, Furst and Griebner: München. med. Wchnschr., July 26, 1910. Quoted by Rosenau: Preventive Medicine and Hygiene, 1918, p. 198.

medium was used in the States by Major F. P. Gay with excellent results.

A brain medium is described in a letter from the director of laboratories.⁷ This consists of brain run through a meat grinder to which is added titered broth or distilled water. Here, however, whole brain medium was still used, for the following reasons: (1) It had already given satisfactory results over a considerable period of time. (2) It was felt that brain, to a certain extent, might prove a selective medium for the meningococcus. In this case it would be an advantage to use the tissue as unadulterated as possible. The addition of broth, for example, would be certain to diminish any selectivity there might be. Some limited work on brain plates was inconclusive on this point. (3) The whole brain medium is much drier than the medium recommended in the letter, and gives a better surface for growth than the "mush" of the latter. Thus, in the whole brain tubes an appreciable amount of spinal fluid may be added without "flooding" the tube. (4) The whole brain is simpler to prepare, requiring only brain tissue, test tubes, and an autoclave. Neither titration nor distilled water is necessary. Thus, it can be made in a few hours in laboratories where the equipment is very elementary.

Transplants were made from the brain medium on laked human blood glucose agar slants. Human blood was laked in two to three parts of sterile distilled water. To 1 per cent. glucose agar slants, neutral to phenolphthalein before autoclaving, 0.25 to 0.50 of 1 c.c. of this lake was added. Later, agar that was 0.3 per cent. acid to phenolphthalein previous to autoclaving was used, with apparently equally satisfactory results. Transplants were made from these slants onto serum-free agar. On this medium some strains grew well at once; some grew at first feebly, but later with considerable abundance; and some refused to grow at all. After from twelve to sixteen hours' incubation, the growth on the laked blood tubes was washed down and agglutinated. The agglutination was repeated on those strains that gave a growth on serum-free mediums.

Varying polyvalent serums were furnished for therapeutic use. Those on hand were run against most of the strains to determine which gave the highest agglutination titer against the particular organism, and therefore might reasonably be supposed to be of the greatest therapeutic value. Since at first no monovalent type meningococcus serums were available, it was felt that the titer of a given organism against a number of polyvalent serums might furnish some

7. Office Letter No. 30; Division of Laboratories and Infectious Diseases, Jan. 7, 1918.

information as to whether these strains were of the same or of different types. The results are shown on Chart 3. Toward the last of October, Rockefeller normal and parameningococcus serums were obtained and, since the first of January, some Pasteur Types A, B and C. By this time, unfortunately, many of the stocks had been lost by contamination. From the first, molds were extremely annoying at this laboratory, spoiling many stock cultures. This was probably due to the character of the light frame buildings.

Agglutinations were set up in dilutions of serum running from 1:50 to 1:200, and sometimes higher, with a normal horse serum control diluted 1:50. Tubes were read after sixteen hours at 55 C. Later, some agglutinations were run according to a method kindly demonstrated to us by Dr. Charles Nicolle, at Pasteur Institute.⁸ To 1 c.c. of a relatively light suspension of organisms (1 cgm. of growth in 20 c.c. of normal salt solution) is added 0.05 c.c. of undiluted serum. The tubes are agitated with considerable violence from one to five minutes and the agglutinations read. This is of particular value in rapid type determination, rather than for quantitative titrations.

Of the nine strains tested with monovalent Rockefeller serum, six were normal meningococcus and three were neither normal nor parameningococcus. Case 15 (Chart 3) agglutinated with Pasteur B, and Rockefeller normal serums. Cases 17 and 18 showed Pasteur B in the throat during convalescence; and in the spinal fluid, Pasteur B and Rockefeller normal. As to the polyvalent serums, Lederle, Rockefeller and Squibb gave fairly consistent agglutinations. Mulford's serum gave an agglutination of 1:200 with five, and no agglutination at 1:50 with six of the strains tested. So Mulford's serum was used only when no other was available. But as far as drawing any definite conclusions as to variations in type from agglutinations with a number of polyvalent serums alone, the results were unsatisfactory. Such variations as are found in the agglutinations with normal and polyvalent Rockefeller serums in Cases 8, 15, 17 and 18, for example, are difficult to explain, since a uniform technic was used.

The West⁹ tubes were not used for nasopharyngeal cultures. In the first place, until very recently, neither sufficient glass tubing nor copper wire were available. In the second place, experience in the States showed that it was very difficult to have tubes, in large quantities, properly bent, and that they were extremely cumbersome to

8. Nicolle, Dedains and Jouan: *Etudes sur des meningocoques et les serums antimeningococciques* (Premier Memoire), *Ann. de l'Inst. Pasteur* **32**: (April) 1918.

9. West: *Proc. Roy. Soc. Med., Otol. Sect.* **4**:43, 1910-1911.

manipulate. Also that they might not serve the purpose for which they were intended; for the function of the glass tubing is to prevent contamination of the swab. During the introduction of the tube into the mouth, the end of the glass may become contaminated with saliva. For this reason it was recommended that during the removal of the tube from the mouth, the swab should not be drawn back into the tube; lest by so doing it also becomes contaminated with the saliva. But the danger of such contamination is no greater during the withdrawal of the swab than during its projection. Besides, it was very difficult to be sure that the tube was well behind the soft palate without touching the posterior pharyngeal wall, thus inducing gagging even before the projection of the swab. The following method, which was adopted here, was suggested by Major F. P. Gay at the department laboratory, Fort Sam Houston, Texas. Stout wire, similar to that which is used to bale hay, is cut into pieces about 20 cm. long, and a centimeter and a half at one end is bent at a little less than a right angle. This is wound with cotton similar to the West tube swab, except that, if the wire is slightly rusted, the end need not be hooked in order to hold the cotton firmly. In taking the culture, a tongue depressor or spoon is necessary. The swab is introduced horizontally. When back of the uvula, the bent end is turned up into the nasopharynx and the swab wiped rapidly down the posterior pharyngeal wall during withdrawal, at which time gagging may occur. The tongue blades may be recovered by boiling and drying in the hot air sterilizer. The swabs are burnt off in the flame of a gasoline torch, rewound, wrapped in paper in bundles of any convenient number and resterilized. This is obviously much more economical in time and materials than blowing glass, annealing copper wire, plugging, sterilizing and cleaning West tubes. Also a much clearer view of the pharynx is obtained, and gagging, when it occurs, takes place after rather than before swabbing.

Nasopharyngeal swabs were inoculated on human laked blood agar plates similar to the slants previously described, except that 0.5 c.c. of the lake was added to each plate. One, two, and sometimes three swabs were put on a plate, according to the pressure of work and the availability of supplies. The plates were kept warm during transportation to the laboratory by means of warm bricks. At the laboratory the inoculated spot, which was always over the blue pencil identification number, was streaked out with a nichrome wire and the plates incubated over night. The next morning suspicious colonies were fished into the fluid medium recommended by Olitsky (horse serum plus broth 1:50) incubated and agglutinated directly in the tube with polyvalent serum. Later this method was discontinued and colonies

were inoculated on to human blood slants, incubated, washed down and agglutinated.

SERUM THERAPY

Our mortality in eighteen cases of meningococcus meningitis was 66 $\frac{2}{3}$ per cent. Patient 3 died on the ninth day of the disease when apparently convalescent. Necropsy showed marked bronchopneumonia with the meningitis in the recrudescence stage. This mortality is more like that given by Flexner⁴ before serum therapy was instituted. In the same paper Flexner emphasizes the fact that serum therapy may fall into disrepute, if inert serums are used, and urges the need of standardization of commercial serums. For this the agglutination titer of the serum is recommended as a standard. The test bleedings should give a titer of 1:200 or higher "for the main normal and paratypes and for the several intermediate varieties used for inoculation" (p. 15). In this series, eight of the patients received a serum, the titer of which was 1:200, or higher, for the organism recovered in each case. Each of these patients received an average of 278 c.c. intraspinally, and 191 c.c. intravenously. Five of the eight patients died, giving a mortality of 62.5 per cent. The mortality among the other ten cases was 70 per cent. Of these ten, the titer of the serum used in one-half of the cases was less than 1:200, and in the other half it was not determined. With such small figures the difference between 62.5 and 70 per cent. is not appreciable and raises the question as to the efficacy of the agglutination titer as a criterion of the therapeutic value of a serum.

Lieut. Bradford F. Dearing, Base Hospital 56, was in charge of all the cases except the first five and Case 10. His method, usually was to give three injections of serum during the first twenty-four hours and after that one every twelve hours, both intrathecally and intravenously, till all symptoms disappeared. For the next few days he gave one intraspinal injection every twenty-four hours. There never was more than a slight margin of safety in the supply of serum. At one time it was so difficult to obtain that a special order was issued forbidding intravenous treatment except with the consent of the chief of the medical service and the medical consultant. This made it impossible to separate the patients into groups and try exclusively one type of serum on each group. Most of the patients received two and some even four kinds of polyvalent serum. The total amounts of each serum used were Squibb 5,045 c.c., Lederle 2,460 c.c., Pasteur 1,280 c.c., Mulford 1,170 c.c., Parke, Davis & Co. 210 c.c., Rockefeller 150 c.c., giving an aggregate of 10,215 c.c., or an average of 573 c.c. per patient. With the exception of Cases 2 and 17, which were

extremely insidious in onset, all cases received their first administration of serum from the first to the fifth day after the onset of symptoms.

All patients but one (Case 5) that died, were necropsied. No case showed any appreciable ventricular dilatation or other evidence of obstruction to the circulation of spinal fluid which would help to account for the poor results. Certainly the treatment was sufficiently energetic, both in frequency and in amount of serum administered, to have given a better mortality.

It was of considerable interest from a clinical standpoint that five, or 27.7 per cent. of the patients showed purpura. Only one of these recovered. The purpura varied from the marked blotchy type in Case 5, in which the patient died within forty-eight hours after onset, to the small pinhead sized hemorrhages in Case 18, in which the patient recovered. Of these five, two showed normal meningococci, one showed neither normal nor parameningococcus, and two were not typed. Netter and Mozer¹⁰ note an increase in purpura among meningococcus meningitis cases to 29.7 per cent. recently, as compared with 2.7 per cent. in a series running from 1908 to 1914.

Finally, then, the cases in this series received considerable amounts of serum fairly early and at frequent intervals, and without any apparent parallelism between mortality and the titer of the serum used. If the titer is an index of the efficiency of a serum, one cannot account for the appalling mortality in this series.

CONCLUSIONS

1. Several of the early cases were evidently infected on arrival at this center.

2. There was absolutely no demonstrable intimate association between any two of the cases.

3. The cases were caused by at least two different types of meningococcus.

4. Due to the occurrence of ten cases at the time of extreme crowding, the stage was set for an epidemic of meningitis. No such epidemic developed.

5. Wholesale culturing has no influence in controlling the spread of meningitis.

6. The "naked" wire swab and tongue depressor are more satisfactory for nasopharyngeal cultures than the West tube.

10. Netter and Mozer: Meningococcus Purpura, Bull. Soc. méd. d. hôp., Paris 42:773 (July 19) 1918.

Case No.	In Camp before Diag- nosis	Location at Onset	Date of Diagnosis	Date of Death	Pur- pura	Type and Amount of Serum Used		Agglutinations								
						Intravenous		Polyvalent			Monovalent					
						Intraspinal	Intravenous	L.	M.	R.	S.	Normal	Para	A.	B.	C.
1	B. H. 56	Sept. 17 (?)	M. 360 S. 360	M. 210 S. 210	1:100*	1:100*					
2	0	E. H. 22	Sept. 20	Sept. 30	S. 230	S. 180	1:100*	1:100*					
3	1 mo.	M. T. C.	Sept. 25	Oct. 3	M. 270 S. 270	M. 210 S. 210	0	1:200	1:200					
4	4 days	B. H. 49	Sept. 29	S. 570	S. 30	1:200	1:200					
5	1 mo.	B. H. 49	Oct. 6	Oct. 8	++	M. 50 S. 50	S. 40	0	1:600	1:600					
6	B. H. 56A	Oct. 24	Oct. 31	S. 480	S. 765	1:200	1:600	1:600					
7	4 days	B. H. 56	Oct. 24	Oct. 31	+	S. 150	S. 180	0	1:100	1:100	0	0			
8	6 days	B. H. 56	Oct. 28	Oct. 31	S. 165	S. 255	1:200	1:100	1:200	1:200	0			
9	8 days	B. H. 25	Nov. 9	Nov. 27	S. 230	S. 455	0	1:100	1:200	1:200	0			
10	4 mo.	B. H. 25	Nov. 9	Nov. 17	+	S. 55	S. 45	1:100	1:100	1:200	1:200	0			
11	12 days	B. H. 56A	Nov. 11	Nov. 26	P. 100 S. 105	P. 140 S. 145	0	0	1:200	1:100	1:100	0			
12	1 mo.	Eng. Sect.	Nov. 15	P. 60 L. 300	L. 420	1:200	1:200	1:200	1:100	1:200	0			
13	4 mo.	B. H. 20	Nov. 16	L. 370	L. 285 subcut. 45	1:200	0	1:200	1:200	1:200	0			
14	2 days	B. H. 49	Nov. 22	Nov. 30	P. 135 L. 160	1:100	1:200	1:200	1:200	1:200	0			
15	1 mo.	Con. Camp	Nov. 22	Dec. 21	R. 150 P. 270	1:100	1:200	1:200	1:200	1:400	0	0	+	0
16	plus 2 wk.	B. H. 97	Dec. 13	Dec. 21	+	S. 150 L. 80	L. 425	1:100	1:100	1:100	0	0	+	0
17	3 wk.	B. H. 70	Dec. 18	P. 365	L. 35	1:100	1:200	1:200	0	0	+	0
18	19 days	B. H. 97	Dec. 29	+	P. 300	L. 100	1:200	1:200	0	0	+	0
						P. D. 110	M. 60 P. D. 100	1:200	1:200	0	0	+	0

Polyvalent serum: L., Lederle; M., Mulford; R., Rockefeller; S., Squibb.
Monovalent serum: Normal and para, Rockefeller; A., B. and C., Pasteur.

7. Whole brain medium is excellent for growing meningococcus, especially from the spinal fluid in cases of diagnostic difficulty, and for preserving stock cultures.

8. Most of the therapeutic serums gave a fair titer against most of the strains of meningococci recovered.

9. Since considerable amounts of serum were administered fairly early, both intraspinally and intrathecally and at frequent intervals, and if the titer of a serum is an index of its therapeutic value, then the extremely high mortality of this series is hard to explain.

10. Finally, the result of the studies in this small series of cases bears out the idea expressed in the title of this paper; namely, that this disease here was a nonepidemic "epidemic" meningitis.

EXPLANATORY NOTES FOR TABLE ON PAGE 735

In camp before diagnosis: Cases 2, 4, 7 and 14 were at the Center four days or less before meningitis was diagnosed. All others were here from six days to four months before the diagnosis, except cases 1 and 6 where the time could not be ascertained.

Location at onset: No hospital or section furnished more than three cases. In other words, no "focus" furnished more than 16.6 per cent. of the cases. The possibility of a "focus" was further eliminated by the element of time lapsing between cases and the lack of any obtainable evidence of association between the cases not separated by time.

Date of diagnosis: The cases here divide themselves into four groups by months as is shown graphically in Chart 1. The exact date of diagnosis of Case 1 could not be obtained.

Date of death: Six out of eighteen cases recovered.

Purpura: Four of the five cases showing purpura died.

Type and amount of serum used: The total amount of serum given intraspinally was 6,005 c.c., or an average of 333 c.c. per case; intravenously 4,500 c.c., or an average of 281 c.c. per case (cases 14 and 15) receiving no intravenous serum because of the special order forbidding it; and 45 c.c. subcutaneously. From one to four serums were used in each case. Squibb's was the only serum used exclusively on any case.

Agglutinations—Polyvalent: The Lederle serum used for agglutination was marked 56H78-H; the Mulford A332929; the Rockefeller, April 26, 1918, except when marked (*) when Jan. 10, 1918, was used; and the Squibb 11862 except when marked (*) when 11635 was used. A zero in the agglutination columns means that the organism did not come down at 1:50. No lower dilutions were run.

Monovalent: The normal and parameningococcus serums were obtained at the Rockefeller Institute, New York, in June, 1918; types A, B and C, at the Pasteur Institute in January, 1919. Of the nine strains run, six were normal and none were parameningococci. Three came down with Pasteur B. Cases 17 and 18 showed this type in the nasopharynx as well as the spinal fluid.

THE CEREBRAL COMPLICATIONS OF MUMPS

WITH REPORT OF NINE CASES

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Mumps is typically a harmless disease. Orchitis, which is the only common complication, usually runs a benign course. At times, however, other complications may occur which make the course of the disease a severe one. Osler mentions the fact that six deaths are recorded in the Index-Catalog of the Surgeon-General's Library as having resulted from mumps. Recently other fatal cases have been reported. Death, when resulting directly from mumps, is probably always due to the cerebral complications.

The fact that involvement of the central nervous system may occur in mumps has long been recognized, the first fatal case having been reported in 1758 by Hamilton. Approximately one hundred and fifty cases of cerebral complications, exhibiting quite a variety of symptoms, have been reported. Acker¹ summarized the literature up to 1913 and added two cases of his own, one with death and necropsy. The nature of the cerebral complications has been much discussed. Before the advent of lumbar puncture it was considered as meningismus, but with the demonstration of a pleocytosis of the spinal fluid it was looked on as a meningitis. In simple mumps, according to Dopter, the spinal fluid is normal.

Many things point to the fact that the fundamental condition is an encephalitis and not simply a meningitis. In most cases the cerebral symptoms are out of all proportion to the meningeal reaction, as evidenced by the pathologic findings in the spinal fluid. The common symptoms are high fever, headache, nausea and vomiting. Usually there is only slight rigidity of the neck and not a well marked Kernig's sign. Numerous cases occur of undoubted involvement of the cerebrum alone, such as Cases 6 and 9 recorded below. In these cases there are no definite meningeal signs and no pathologic findings in the spinal fluid. Among the symptoms noted in the thirty-one cases

1. Acker, G. N.: Parotitis Complicated with Meningitis. *Am. J. Dis. Child.* 6:399 (Dec.), 1913.

reported by Acker were unilateral convulsions, monoplegia, hemiplegia, aphasia, speech disturbances, psychosis, disturbances of sensation and stupor. Such symptoms point to a true involvement of the brain substance. The other predominant symptoms, such as bradycardia, headache, vomiting and optic neuritis are probably the direct result of increased intracranial pressure. Unfortunately, the spinal fluid findings are recorded in only three instances. Larkin² describes two cases of cerebral complications subsequent to mumps. One patient had paralysis of the left arm and right leg, suggesting an encephalitis. The spinal fluid was normal. The few necropsies which have been recorded have shown very marked congestion of the brain with only a serous meningitis.

Recently nine cases of mumps with cerebral complications were observed in the base hospital at Camp Lee. During the time covered by this report, 476 cases of mumps had been admitted to the hospital. The patients with complications exhibited a fairly uniform symptom complex. Usually, as the parotitis is subsiding, there is a marked rise in temperature, with little change in pulse rate, severe headache, nausea and vomiting. Often the patient has an orchitis. On examination, the patient is dull, answers questions slowly, shows slight stiffness of the neck, a suggestive Kernig's sign and variable reflexes. Lumbar puncture shows a clear fluid with a lymphocytosis and under increased pressure. I do not believe that the number recorded in this series shows the true percentage of cerebral involvement. Often patients have been observed with severe headache and fever, sometimes with vomiting, occurring in the course of mumps. There are no other signs of meningitis and nothing is found elsewhere to account for the symptoms. Many such cases are really cases of a mild encephalitis. This conclusion is based on the similarity of the symptoms in these cases with those seen in cases in which a definite cerebrospinal involvement is evidenced by the pleocytosis of the spinal fluid and on the absence of findings elsewhere to explain the symptoms. No record has been kept of the number of such cases. Lumbar puncture has been done in a few instances with negative results, except for increased pressure.

A recent report³ on 5,756 cases of mumps occurring in an army camp does not mention meningitis or encephalitis among the complications observed, although mention is made of the fact that nausea,

2. Larkin, W. R.: Mumps-Meningitis; Report of Two Cases with Necropsy Findings, *Mil. Surgeon* 44:92 (Jan.), 1919.

3. Radin, M. J.: The Epidemic of Mumps at Camp Wheeler, *Arch. Int. Med.* 22:324 (Sept.), 1918.

vomiting, pain and tenderness of the testicles have been noted as occurring without apparent reason. Many such cases are due to localization of the infection in the central nervous system.

SUMMARY OF SPINAL FLUID FINDINGS

	Pres- sure	Macro- scopic Appear- ance	Total White Blood Cell Count	Differential Count	Glob- ulin	Sugar	Smear	Cul- ture	Was- ser- mann
Case 1— First puncture....	Olear	230	Polymorpho- nuclears 42%, mononu- clears 58%	0	..	0	0	...
Second puncture*	Clear	400	Polymorpho- nuclears 71%, mononu- clears 29%	Trace	..	0
Third puncture...	Clear	158	Polymorpho- nuclears 37%, mononu- clears 63%	0	..	0	...	0
Case 2— First puncture....	++	Clear	330	Not done	0	..	0	0	...
Second puncture..	Clear	780	Polymorpho- nuclears 40%, mononu- clears 60%	Trace	..	0	0	...
Case 3.....	++	Clear	75	Large mono- nuclears 4%, small mono- nuclears 96%, polymorpho- nuclears 0	0	..	0	0	0
Case 4.....	Normal	Clear	220	Small mono- nuclears 82%, polymorpho- nuclears 0, large mono- nuclears 18%	0	..	0	0	...
Case 5 †.....	++	Clear	67	Large mono- nuclears 52%, small mono- nuclears 48%, polymorpho- nuclears 0	0	+	0	0	...
Case 6— First puncture....	++	Clear	10	Small mono- nuclears 100%	0	+	...	0	...
Second puncture..	++	Clear	5	Small mono- nuclears 100%	0	+	0	0	...
Case 7.....	+	Clear	125	Mononuclears 100%	0	+	0	0	...
Case 8 †.....	++	Slightly turbid	440	Mononuclears 100%	+	+	See ‡ note	0	...
Case 9.....	++	Clear	3	Mononuclears 100%	0	+	0	0	0

* Ten per cent. antimeningococcus serum given day before.

† Colloidal gold reaction 0000000000.

‡ Smear showed few gram-positive cocci. No growth could be obtained. Rabbits injected intraspinaly were negative.

In the cases observed here there was seldom any question as to the nature of the infection. In the first case, tuberculous meningitis was considered, the patient having been admitted with symptoms pointing to a meningitis which had developed before the submaxillary swelling was recognized.

Smears and cultures were made from the spinal fluid in all cases. Gram-positive cocci were found in smears from the fluid in Case 8.

This fluid was turbid when withdrawn. Rabbits were injected intraspinally with a mixture of the fluid and normal horse serum with negative results. No growth was obtained from cultures. Gram-positive cocci have been described by several observers as the organism causing the disease, although Wollstein considers that it is due to a filterable virus.

Lumbar puncture has proven an effectual therapeutic agent. The temperature usually falls to normal quickly, and the headache is relieved following the withdrawal of fluid.

SUMMARY

Nine cases of cerebral complications occurring among 476 cases of mumps are recorded.

The cerebral complication is probably mainly an encephalitis instead of a meningitis.

Gram-positive cocci have been demonstrated in the spinal fluid of one case. Animal inoculation and culture were negative.

Lumbar puncture is a most effectual therapeutic measure.

CASE REPORTS

CASE 1.—A private, 572, Casual Co., aged 36, white, was admitted to the hospital Jan. 5, 1919, complaining of fever, headache and vomiting.

Personal History.—He had measles when a child, typhoid fever in 1913, and influenza at Camp Upton in 1918. He has never had mumps. The patient has been a moderate user of alcohol.

Present Illness.—This began with vomiting and fever. The patient vomited intermittently for three days and complained of fever, headache, pain in the back, loss of appetite and an unproductive cough.

Examination.—The patient did not seem to be in ill health, but his temperature was 103.4 F., pulse 104, respiration 24. He was a well-developed, muscular man. There was no eruption on the skin. The heart, lungs and abdomen were negative. The patient was rather cyanotic; his head was retracted; the neck was slightly rigid and Kernig's sign was suggestive. Forty c.c. of spinal fluid were removed and 10 c.c. of antimeningococcus serum were injected. The spinal fluid contained 230 cells per cubic millimeter. Differential count: polymorphonuclears, 58 per cent.; mononuclears, 42 per cent.; globulin negative; smear and culture negative.

Clinical Course.—The following day there was very marked enlargement of the submaxillary glands without swelling of the parotids. The patient no longer complained of headache or stiffness of the neck, although Kernig's sign was still suggestive. Spinal puncture gave a clear fluid with a cell count of 400 per cubic millimeter. Differential count: polymorphonuclears, 71 per cent.; mononuclears, 29 per cent.; globulin and smear, as well as Wassermann test, negative. Cultures from the nasopharynx were negative for meningococci on two occasions. The temperature ranged between 100 and 102 F., with an average pulse of 80, until January 12, when both temperature and pulse dropped to normal. The submaxillary swelling continued for a week. The patient made an uneventful recovery and was discharged to duty.

CASE 2.—A private, Company D, 62d Infantry, aged 25, white, was admitted to the hospital Jan. 6, 1919, because of swelling in the face.

Personal History.—The patient had varicella, pertussis and scarlet fever during childhood.

Present Illness.—He became ill on the morning of admission to the hospital with soreness and swelling of the jaws.

Clinical Course.—When first seen the patient had swelling of both parotids. For the following two days his temperature ranged between 99 and 100 F.; then it fell to normal and remained so until January 17, when it rose to 100.2 F. January 18, the temperature was 103 F., with a pulse of 90. He also complained of headache.

Examination.—There was slight stiffness of the neck with a suggestive Kernig's sign. The white blood cells numbered 15,800. Lumbar puncture gave a clear fluid under increased pressure. The spinal fluid contained 330 cells per cubic millimeter; it was free from globulin; smear and culture were negative. January 19, the white blood cells numbered 10,500; blood culture was negative. Lumbar puncture gave a clear fluid; 40 c.c. of antimeningococcus serum were injected intraspinally. The spinal fluid contained 780 cells per cubic millimeter. Differential count: polymorphonuclears, 40 per cent.; mononuclears, 60 per cent.; trace of globulin; smear and culture negative. The temperature on this day did not go above 102.2 F. It fell to normal on the following day and remained so. All symptoms rapidly disappeared and the patient was discharged to duty.

CASE 3.—A corporal, Company M., 66th Infantry, aged 24, white, was admitted to the hospital Jan. 22, 1919.

Personal History.—The patient had had measles, pertussis, varicella, pneumonia and typhoid in childhood.

Present Illness.—This began the day before admission with pain under the left ear.

Clinical Course.—On admission the patient had a swelling of the left parotid. The temperature was 101 F., pulse 108, respiration 22. January 26, the right submaxillary gland became swollen. January 29, a left sided orchitis developed. The temperature rose to 104 F.; pulse 96.

Examination.—January 30, the patient appeared to be dull, pupils equal and active; he had a severe headache for two days. There was no evidence of cranial nerve paralysis. The leg could not be extended fully on the flexed thigh; knee jerks were diminished; the plantar and abdominal reflexes were present. The Brudzinski sign was negative. Lumbar puncture showed the spinal fluid to be under increased pressure. It contained 75 cells per cubic millimeter. Differential count: small mononuclears, 96 per cent.; large mononuclears, 4 per cent.; globulin and smear negative. The leukocyte count was 8,200. After withdrawal of the spinal fluid the temperature returned to normal and all the symptoms rapidly disappeared. The patient was discharged to duty February 8.

CASE 4.—A private, Company D, Eighth Ammunition Train, aged 22, white, was admitted to the hospital Jan. 25, 1919.

Personal History.—He had measles and rheumatic fever seven years ago.

Present Illness.—This began with soreness and swelling behind the angle of the jaws two days before admission.

Clinical Course.—The patient evidently had a bilateral parotitis. His temperature was 99 F., pulse 70. January 25, he began to have headache and developed a slight swelling and tenderness of the right testicle. January 31, a slight stiffness of the neck was noted; there was no Kernig's sign or any other symptom. Lumbar puncture gave a clear fluid under normal pressure, containing 220 cells per cubic millimeter. Differential count: small mononuclears, 82 per cent.; large mononuclears, 18 per cent.; globulin and smear negative. The urine was likewise negative. The temperature at this time

was 103 F., pulse 74, respiration 16. The temperature remained high until February 2. All symptoms were relieved by lumbar puncture and the man was discharged to duty February 7.

CASE 5.—A corporal, Company B, 62d Infantry, aged 21, white, was admitted to the hospital Jan. 27, 1919, complaining of swelling of the right side of the face.

Personal History.—He had measles in childhood, pneumonia in 1915 and influenza in 1918.

Present Illness.—This began the day of admission with swelling of the right side of the face.

Clinical Course.—On admission of the patient the right parotid was swollen; temperature was 100.6 F., pulse 86, respiration 18. February 3, a swelling of the right testicle was noted. The temperature ranged between 102 and 103 F. from February 3, to February 6. The patient had a severe headache all the time, but was free from nausea and did not vomit. February 6, there was a slight stiffness of the neck and Kernig's sign was suggestive. Reflexes active and equal; other signs were absent. Lumbar puncture gave a clear fluid under very much increased pressure. It contained 67 cells per cubic millimeter. Differential count: large mononuclears, 52 per cent.; small mononuclears, 48 per cent.; globulin, negative; sugar, positive. The colloidal gold reaction was 0000000000. The leukocyte count on February 5, was 8,900. Differential count: large mononuclears, 8 per cent.; small mononuclears, 18 per cent.; eosinophils, 1 per cent.; polymorphonuclears, 7 per cent. The urine was negative. The following day the temperature rose to 102 F., then it fell to normal and remained so. The left parotid became swollen February 8. The headache disappeared rapidly after lumbar puncture and the patient made an uneventful recovery.

CASE 6.—A wagoner, Quartermaster's Corps, detached, aged 21, white, was admitted to the hospital Feb. 3, 1919, complaining of headache and swelling of the neck.

Personal History.—He had measles and pertussis and in October, 1918, he had an attack of influenza.

Present Illness.—Three weeks ago he first noticed a swelling on the right side of the neck and under the jaw. He now complains of headache and occasional nausea.

Clinical Course.—On admission the right submaxillary glands were swollen; the temperature and pulse were normal. February 5, the left parotid became swollen and on February 9, bilateral orchitis was noted. February 10, the patient became very dull and suffered from headache and vomiting. The temperature was 105 F., pulse 180, respiration 20. February 11, the patient began to be very drowsy and was still vomiting. There was definite stiffness of the neck, although the pupils were active. The knee jerks were not obtainable and the right biceps reflex was barely noticeable. Kernig's sign was positive; the Babinski was negative. Lumbar puncture gave a clear fluid under increased pressure. There was marked improvement in the patient's condition immediately afterward. February 13, the pulse was only 48 and the temperature was subnormal. The patient stated that he could not see well. During the night he became so delirious that he had to be restrained. February 14, he appeared to be in a stupor and his head was retracted; the pupils reacted sluggishly; neither headache nor vomiting were present. The temperature was 97 F., pulse 44, respiration 16. Deep reflexes could not be elicited and the Babinski was negative. Lumbar puncture gave a clear fluid. The next day the patient was markedly improved. He made a rapid recovery and was discharged.

Laboratory Findings.—February 6, the urine was negative. February 12, the leukocyte count was 6,200. Differential count: small mononuclears, 48 per cent.; large mononuclears, 6 per cent.; eosinophils, 5 per cent.; polymorphonuclears, 41 per cent. February 11, the spinal fluid contained 10 cells per cubic millimeter, all being mononuclears; the globulin was negative but the sugar was positive. Culture and smear were both negative. February 14, the spinal fluid contained only 5 cells per cubic millimeter, they were all small mononuclears. The globulin and culture tests were negative, but the sugar test was still positive.

CASE 7.—a private, Company B., S. A. T. C., University of Virginia, aged 19, white, was admitted to the hospital Dec. 21, 1918.

Personal History.—He has not had any infectious diseases.

Present Illness.—He had an attack of influenza beginning Dec. 21, 1918. Jan. 7, 1919, he developed measles and this was followed by an acute hemolytic streptococcus tonsillitis. February 6, his temperature rose and the submaxillary glands on both sides became enlarged.

Clinical Course.—February 7, orchitis was noted; the temperature remained elevated, averaging 103 F., until February 9. On that day the patient was very restless and uncomfortable and had vomited everything for twenty-four hours. He did not complain of headache. Examination showed some resistance on flexion of the neck and Kernig's sign was positive; the cranial nerves were negative; the deep reflexes were not obtained; there was no clonus. The temperature was 104.3 F., pulse 96, and respiration 24. Lumbar puncture gave a clear fluid under somewhat increased pressure. The puncture relieved all symptoms. The temperature dropped to normal and recovery was uneventful. The parotid glands were not involved at any time during the disease. The patient was discharged to duty February 25.

Laboratory Findings.—February 12, the leukocytes numbered 8,100. Differential count: small mononuclears, 26 per cent.; large mononuclears, 6 per cent.; polymorphonuclears, 66 per cent., and eosinophils, 2 per cent. The urine contained a faint trace of albumin, but was negative otherwise. The spinal fluid contained 125 cells per cubic millimeter, all being mononuclears. The globulin test, smear and culture were negative.

CASE 8.—A private, Company 11, Third Battalion, 155 D. B., aged 24, white, was admitted to the hospital March 2, 1919, complaining of swelling of the left side of the face.

Personal History.—He had had the usual eruptive fevers in childhood, and pneumonia in 1918.

Present Illness.—This began the day before his admission to the hospital with swelling and pain on the left side of the face.

Clinical Course.—Only the right parotid was swollen on admission. The temperature was 100.8 F., pulse 100, respiration 20. March 5, the left parotid became involved. The temperature fell to normal. March 6, the patient complained of severe headache. This continued for two days with a temperature as high as 103.6 F. March 8, the patient complained of severe headache and he was vomiting. There was no evidence of orchitis. The parotid enlargement had practically disappeared, but there was definite stiffness of the neck, with slightly positive Kernig's sign. The patient's facial expression was dull. The cranial nerves were negative and the deep reflexes were not obtainable, except the left biceps tendon reflex. The Babinski was negative; there was no clonus. Lumbar puncture gave a slightly turbid fluid under increased pressure. Following the puncture the temperature rapidly returned to normal and all symptoms cleared up. Recovery was uneventful and the patient was discharged to duty March 17. The spinal fluid contained 440 cells per cubic millimeter. Differential count: mononuclears, 100 per cent.; mostly small cells. The sugar and the globulin tests were positive. A few gram-positive cocci

were obtained in the smear but all the cultures were negative. No results were noted from the intraspinal injection. The urine was likewise negative.

CASE 9.—A private, Company M, 66th Infantry, aged 32, white, was admitted to the hospital March 6, 1919, because of swelling of the face.

Personal History.—This is unimportant as it had no bearing on the case.

Present Illness.—The day before admission the patient noted a soreness and swelling on both sides of the face.

Clinical Course.—On admission a bilateral parotitis was present and the patient complained of headache. His temperature was 100.2 F., pulse 88, respiration 22. The temperature fell to normal but on March 12, it rose to 104.6 F., and remained high, with relative bradycardia, for the succeeding forty-eight hours. The patient complained of pain in the testicles but there was little objective evidence of orchitis. He had a severe headache and vomited a number of times. March 13, he was very dull. There was rather marked stiffness of the neck, but the Babinski and the Kernig signs were negative. The deep reflexes could not be obtained, except that of the right biceps. Lumbar puncture gave a clear fluid under increased pressure but neither the headache nor the vomiting were relieved by the puncture, nor did the temperature drop. March 14, at 4 p. m., the temperature was 105.4 F., pulse 80, respiration 24. Two hundred and fifty c.c. of a 25 per cent. glucose solution were injected. In a few minutes the patient was chilled and the temperature rose to 106.6 F. Delirium set in with convulsive twitchings of the muscles and restraint had to be used to keep the patient in bed. The headache disappeared. The following day the patient was still very dull, weak and incontinent. The eye grounds were negative, except for a slight haziness of the disks on the nasal side. Hiccup was present for several hours. March 15, at 8 a. m., the temperature was 98.8 F. and it was normal thereafter. The patient was weak for a while, but is recovering rapidly and will be discharged to duty soon.

Laboratory Findings.—March 13, the spinal fluid contained 3 cells per cubic millimeter, all being mononuclears. The globulin test was negative and the sugar test was positive. Smear, culture and urine examination and Wassermann test were all negative.

THE OXYGEN CONSUMPTION OF HUMAN ERYTHROCYTES*

GEORGE A. HARROP, JR., M.D.

BALTIMORE

The earlier work on the respiratory metabolism of the blood itself was in large part rendered valueless because of lack of knowledge of the growth of micro-organisms; the effects observed being merely due to bacterial action.¹ It has been shown, however, by Warburg, and by Morowitz and his pupils, that each of the principal formed elements of the blood, leukocytes, erythrocytes, and platelets, has, under certain circumstances, a measurable oxygen consumption.

Studies of the oxidative properties of nucleated and unnucleated erythrocytes were made by Warburg² in 1909. He determined the oxygen capacity of defibrinated blood with the Barcroft-Haldane apparatus, and redetermined the oxygen absorption which had taken place after incubation at body temperature for a period, protected from the air. Normal human blood consumed very little oxygen, the amounts absorbed during short periods of incubation being less than the margin of experimental error, while the changes in blood left for longer periods were small, and could be attributed to the metabolism of the leukocytes. Somewhat higher values were found in the blood of rabbits, particularly in the young. In contrast to the minimal oxygen absorption in the blood of normal adult mammals, that of the nucleated erythrocytes of birds was found to be very high.

Morowitz³ studied the oxygen absorption in the blood of rabbits made anemic by repeated venesection and by injection of hemolytic agents, such as phenylhydrazin. He found that under certain conditions the oxygen absorption could be so increased that the entire quantity in the blood was consumed in fifteen minutes. He presented evidence to show that this absorption was due to the formed elements of the blood, not to substances in the plasma, that it could not be accounted for by the nucleated cells of the blood, either red or white, but that, in short, it was due to the young, unnucleated red cells which were present in large numbers in these experimental anemias.

*From the Medical Clinic of the Johns Hopkins Hospital.

1. The older literature is summarized by Zuntz in Hermann's *Handbuch der Physiologie* 4:2 (Leipzig, 1882).

2. Warburg, O.: *Ztschr. f. physiol. Chem.* 59:112, 1909.

3. Morowitz, P.: *Arch. f. exper. Path. u. Pharmacol.* 60:298, 1909. Also. *Ergebn. d. inn. Med. u. Kinderh.* 11:277, 1913.

Morowitz and Itami⁴ measured the oxygen absorption in the blood of seventeen persons suffering from various types of anemia. They found a marked absorption in the blood from certain of their patients, but not in that from others. They claimed that while it took place in specimens showing histologic evidences of regeneration, it was found as well in anemias showing none. They concluded that the demonstration of increased oxygen absorption was a most accurate index of blood regeneration, more delicate than microscopic evidence, and that the results were quantitative. The criteria which they considered indicative of regeneration microscopically were the presence or absence of nucleated erythrocytes and of polychromasia. But there was no parallel found either in the severity of the anemias or in the extent or character of the histologic change present, compared to the amount of oxygen absorbed. Loewy⁵ suggested, in the light of Onaka's⁶ observation, that incomplete separation of the platelets in the process of defibrination might account for the inconstant results.

There is now good evidence that the red cells in the circulating blood, which appear reticulated when stained in fresh preparations with brilliant cresyl blue, are youthful erythrocytes. The reasons for this belief are, in the first place, that increased bone-marrow activity, as indicated by a rise in the number of red cells and in the percentage of hemoglobin, is accompanied by a parallel increase in the percentage of these cells in the blood; and, in the second place, that a large percentage of all of the unnucleated red blood cells in the bone marrow are reticulated. We have studied the oxygen absorption in the blood of persons suffering from various types of anemia, and have compared it with the concentration of reticulated cells, as well as with other abnormal findings in the blood, in an effort to correlate the oxygen consumption, if any, which occurs in human anemia with the other available findings.

TECHNIC

The method used for estimating the reticulated cells was that of Robertson.⁷ This gives well stained and well distributed preparations. One thousand cells were counted in each case and the percentage determined therefrom.

For the determination of the blood oxygen, the blood gas apparatus devised by Van Slyke was employed.⁸

The manipulations have been done with strict attention to sterile technic. Each blood sample was withdrawn by venepuncture with a dry syringe and needle and placed in a cotton-stoppered flask of about 50 c.c. capacity, con-

4. Morowitz, P., and Itami, S.: *Deutsch. Arch. f. klin. Med.* **100**:191, 1910.

5. Loewy, A.: *Oppenheimer's Handbuch der Biochemie. Ergänzungsband*, **4**:229, 1913.

6. Onaka, M.: *Ztschr. f. physiol. Chem.* **71**:193, 1911.

7. Robertson, Oswald H.: *J. Exper. M.* **26**:221, 1917.

8. Van Slyke, D. D.: *J. Biol. Chem.* **33**:127, 1918.

taining several glass beads. Simultaneously, a specimen was taken for counting the reticulated cells. The blood sample in the small flask was defibrinated by shaking gently for ten minutes. The fluid blood was then poured off into a wide-mouthed tube, care being taken not to carry over any of the clot or beads. In this it was thoroughly saturated with oxygen.

A portion was then analyzed for its oxygen content while the remainder was used to fill a small specific gravity bottle (Gay-Lussac) of about 5 c.c. capacity, which contained a glass bead for shaking. This type of container was found preferable to one in which the cover sealed off the contents completely from the air. The open capillary in the ground glass stopper permitted complete filling, and compensated for the changes in volume at varying temperatures, while the amount of air absorbed through the long column of the capillary was negligible. The stopper was paraffined in and the bottle incubated at 37 C. for six hours. At the end of this time the material was cooled again to room temperature. After thorough shaking to insure even distribution of the cells, the blood oxygen was again determined by removing the paraffined top, plunging the pipet to the bottom of the bottle and using the lower layer of blood. The remainder was then fully resaturated and the oxygen capacity redetermined.⁹ The original oxygen capacity of the blood and the amount absorbed during incubation enabled one to calculate the percentage of the total oxygen consumed by the blood itself under the conditions of the experiment.

EXPERIMENTAL DETAILS

1. *Other Sources of Oxidation.*—Since it is desired to measure the oxygen metabolism of the erythrocytes alone, it is necessary to exclude other possible sources of oxygen absorption in the blood.

a. Leukocytes.—The oxygen absorption in the blood in conditions where abnormally active regenerative processes are taking place is not referable to moderate variations in the white cell content. Grafe¹⁰ has reported, however, that marked absorption takes place in conditions where the white cells are enormously increased, as in the leukemias, and that it is proportional to the concentration of leukocytes present.

This intense oxygen consumption by the blood in leukemia is demonstrated in the following example:

Jan. 31, 1919. B. S. Diagnosis: Chronic myeloid leukemia. White blood cells 197,000 (peripheral). White blood cells 93,000 (after defibrinating). Reticulated erythrocytes 12 per cent.

	Volume. Per Cent.
Oxygen capacity of blood.....	17.39
After six hours' incubation.....	7.31

Amount absorbed 9.99 or 57.7 Per Cent.
Capacity of incubated sample when resaturated. 16.94 volume per cent.

It is apparent that the concentration of leukocytes must be reduced to a minimum. The method of defibrinating as described is usually

9. In a number of instances this was done colorimetrically by the Palmer method.

10. Grafe, E.: Deutsch. Arch. f. klin. Med. 102:406. 1911.

effective in lowering the leukocyte concentration in the material to 3,000 per cubic millimeter or less, when the count in the peripheral blood does not exceed 8,000 per cubic millimeter. Where the count, after defibrinating, is higher, resort must be had to centrifuging and washing the red blood cells repeatedly with isotonic salt solution. The technic in the experiments here described has been controlled by leukocyte counts after defibrination. Samples of sterile normal blood containing 3,000 leukocytes or less which have been defibrinated by the method described, do not absorb an amount of oxygen exceeding the limit of the experimental error in the period used for incubation.

b. Blood Platelets.—Our attention was called to the blood platelets as a factor in the consumption of oxygen by the blood by observing the marked absorption in oxalated human arterial blood, as compared to that in defibrinated and saturated venous blood. Both specimens were treated with an equal quantity of sodium oxalate, and the only difference lay in the removal of the blood platelets with the clot in the specimen which had been defibrinated. The same effect has been pointed out by Onaka,⁶ working with rabbit's blood. Defibrination effectively removes the platelets; smears taken from the defibrinated material show practically complete absence of these elements. They are caught up in the clot and eliminated.

c. Sources of Oxidation in the Blood Serum.—Barcroft¹¹ has pointed out the possibility of two distinct types of oxidative processes in the blood. In the first place there may be substances, incomplete products of metabolism, which have found their way into the blood stream from the tissues and are there oxidized. In the second place, there is the call for oxygen which may be attributed to the life processes of the corpuscles of the blood itself. Sound evidence is now available that the first type of oxidative processes does not take place in the blood or lungs. Even in conditions of extreme oxygen want,¹² such oxidations as are carried out are completed in the tissues. The oxygen absorption of blood from which the serum had been removed and the corpuscles well washed and suspended in normal salt solution, has been compared with that of the untreated, defibrinated blood sample in which the leukocyte count was properly controlled. The amount of oxygen absorbed is constantly the same. The following experiment will serve as an example:

11. Barcroft, J.: *The Respiratory Function of the Blood*, Cambridge, 1914, p. 120.

12. Evans, C. L., and Starling, E. H.: *Jour. Physiol.* **46**:413, 1913. See also Morawitz, P.: *Deutsch. Arch. f. klin. Med.* **103**:253, 1911; Henriques: *Biochem. Ztschr.* **71**:481, 1915 (reference quoted by Lusk, *Science of Nutrition*, 1917, p. 418).

HARROP—ERYTHROCYTES AND OXYGEN

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March 7, 1919. S. H. Diagnosis: congenital hemolytic jaundice.

Oxygen capacity of defibrinated blood.....	Volume, Per Cent.
After six hours' incubation:	
Whole defibrinated blood.....	11.58
Washed corpuscles suspended in 0.8 per cent. salt solution	8.33
Capacity of incubated sample of whole blood when resaturated	8.42
Capacity of incubated sample of corpuscle suspension when resaturated	11.53
	11.39

d. Errors in the Technic.—Aside from gross errors in the manipulations, these arise chiefly from two sources: bacterial contamination and methemoglobin formation. The danger from bacterial contamination has been avoided by plating the blood residues on glucose agar, thus demonstrating their sterility. The possibility of methemoglobin formation has been eliminated by resaturating with air a portion of the blood sample after incubation, determining afresh the oxygen capacity of the blood, which should and does agree with the original value.

2. Effect of Temperature.—The maximum consumption takes place at 38 C. The consumption is negligible at 7 C. or lower. The following experiment is an example:

S. H. Oxygen capacity at start.....	Volume, Per Cent.	Volume, Per Cent.
Incubation for six hours at 37 C.....	16.21	Absorbed
Incubation for six hours at 21 C.....	14.97	
Incubation for six hours at 7 C.....	15.45	1.24
	16.04	0.76
		0.17

The viability of the cells, as indicated by their ability to absorb oxygen, however, is not destroyed by standing twenty-four hours in the cold (7 C.) and then incubating as usual at 38 degrees for six hours:

S. E. Oxygen capacity at start.....	Volume, Per Cent.	Volume, Per Cent.
Incubation for six hours at 38 C.....	12.16	Absorbed
After standing twenty-four hours at 7 C., then incubating for six hours at 38 C.....	7.90	4.26
	8.43	3.73

3. Integrity of the Cells.—The effect of destruction of the cell bodies on the oxygen absorption was studied by hemolysis of the blood with distilled water:

Oxygen content at start.....	Case 1 Volume, Per Cent.	Case 2 Volume, Per Cent.
After six hours' incubation:		
Whole blood	17.13	6.12
Corpuscles in 0.8 per cent. saline.....	16.28	5.26
Hemolyzed by suspension in distilled water	16.10	5.13
Reaerated whole blood.....	17.06	6.03
	17.24	6.30

By laking the corpuscles their properties as living cells are presumably destroyed. Correspondingly, there was no oxygen absorption in the hemoglobin solution thus incubated, the oxygen content at the end being practically that at the start. Both whole blood, and intact corpuscles suspended in 0.8 per cent. saline, as controls, however, lost oxygen in equal degree.

TABLE 1.—THE OXYGEN CONSUMPTION OF NORMAL HUMAN ERYTHROCYTES. SPECIMENS OBTAINED FROM INDIVIDUALS WHOSE BLOODS GAVE NORMAL ERYTHROCYTE AND LEUKOCYTE COUNTS, NORMAL DIFFERENTIAL COUNTS, AND 1.0 PER CENT. OR LESS OF RETICULATED ERYTHROCYTES

Case No.	Oxygen Content of Saturated Blood	Oxygen Content after Six Hours' Incubation	Oxygen Consumption	Percentage of Reticulated Cells	Leukocyte Count of Specimen as Incubated	Diagnosis
1	20.67	20.54	0.13	1.0	900	Chronic arthritis
2	20.62	20.38	0.24	0.9	1,800	Chronic sinusitis
3	20.50	20.34	0.16	0.9	1,600	Chronic myocarditis (compensated)
4	19.86	19.49	0.37	0.6	1,675	Rheumatic endocarditis
5	21.20	21.10	0.19	1.0	1,300	Normal
6	19.60	19.42	0.18	0.5	2,800	Cardiospasm
7*	24.58	24.42	0.16	0.6	2,100	Erythrocytosis due to chronic cardiac disease, R. B. C. 6,100,000
8*	27.44	27.05	0.39	1.0	1,400	Erythemia, R. B. C. 7,750,000

* These patients had high erythrocyte counts. The blood examination was otherwise normal.

EXPERIMENTAL

In Table 1 are recorded the results of incubating defibrinated blood from individuals where blood smears presented no microscopic abnormalities and where there was a normal percentage of reticulated cells. The last two are from persons with increased red cell counts, but with blood which appeared otherwise normal. All of these determinations showed no changes exceeding the limits of error of the method, and hence the amount of oxygen consumption in these bloods was too small to be estimated. It can be concluded that the erythrocytes of normal blood have no appreciable consumption of oxygen.

TABLE 2.—THE OXYGEN CONSUMPTION IN THE BLOOD OF PATIENTS WITH ANEMIA WITHOUT INCREASES IN THE PERCENTAGE OF RETICULATED CELLS

Case No.	Oxygen Content of Saturated Blood	Oxygen Content after Six Hours' Incubation	Oxygen Consumption	Percentage of Reticulated Cells	Diagnosis
1	9.25	9.10	0.15	0.8	Carcinoma of colon with metastases
2	4.54	4.57	1.0	Pernicious anemia; no histologic evidence of regeneration
3	13.36	12.98	0.38	0.8	Chronic nephritis with uremia
4	15.53	15.37	0.15	0.9	Syphilis; aortic insufficiency
5	17.82	17.38	0.44	0.5	Hypertensive cardiorenal disease

Table 2 gives the results of observations on blood samples from patients with anemia, but with no increase in the percentage of reticulated cells. There was no measurable oxygen absorption.

TABLE 3.—THE OXYGEN ABSORPTION AND THE PERCENTAGE OF RETICULATED ERYTHROCYTES IN A CASE OF PRIMARY ANEMIA DURING A SPONTANEOUS REMISSION

Date	R.B.C. Millions (Peripheral Blood)	W.B.C. (Peripheral Blood)	Oxygen Capacity, Vol. Per Cent.	Oxygen Content after Six Hours, Vol. Per Cent.	Oxygen Consumed Vol. Per Cent.	Per Cent. Absorbed	Per Cent. of Reticulated Cells	Other Microscopic Evidence of Regeneration
11/26/18*	1.5	3,000	6.40	6.23	0.17	1.0	Very few platelets; no myelocytes; no blasts
12/20/18	2.5	7,200	10.31	9.23	1.08	10.5	3.2	Platelets small and few; occasional blast
12/31/18	3.3	8,000	15.05	13.47	1.58	10.5	2.7	Platelets increased; myelocytes and blasts present
1/14/19	3.6	7,800	15.86	14.03	1.83	11.5	3.0	Myelocytes, 2.0 per cent.; occasional nucleated red
1/28/19	3.93	6,200	16.67	15.39	1.28	7.6	2.0	Platelets small, diminished; no blasts
2/19/19	4.6	7,400	17.79	17.67	0.12	0.5	Platelets small, about normal number; red count and hemoglobin stationary since February 10
2/24/19	4.3	6,700	17.40	17.16	0.24	0.4	

* About December 6 patient commenced to feel better and stronger, and during the six days following the erythrocyte count rose by 500,000.

TABLE 4.—THE OXYGEN CONSUMPTION IN BLOOD CONTAINING INCREASED PERCENTAGES OF RETICULATED ERYTHROCYTES

Case No.	Oxygen Content of Saturated Blood Vol. per Cent.	Oxygen Content after Six Hours' Incubation Vol. per Cent.	Oxygen Consumption Vol. per Cent.	Percentage of Oxygen Consumed	Percentage of Reticulated Erythrocytes	Diagnosis
1	18.95	17.67	1.28	6.8	2.0	Carcinoma of stomach
2	9.80	8.84	0.96	9.8	2.0	Chronic empyema
3	17.50	16.28	1.22	7.0	2.3	Pernicious anemia
4	12.61	11.84	0.77	6.1	2.5	Three days after large hemorrhage from gastric ulcer
5	11.62	10.73	0.89	7.7	2.6	Hodgkin's disease
6	14.07	12.51	1.56	11.1	3.4	Ruptured ovarian cyst
7	4.60	4.10	0.50	10.9	4.5	Chronic nephritis; uremia; hemorrhage from gums
8	6.12	5.13	0.99	16.3	7.1	Pernicious anemia
9	11.58*	8.33	3.25	28.1	12.0	Congenital hemolytic jaundice
10	11.48*	8.06	3.42	29.8	12.0	Congenital hemolytic jaundice
11	12.16	7.72	4.44	36.5	13.1	Congenital hemolytic jaundice

* Specimens 9 and 10 are from the same case, with about one month's interval between the two observations.

The observations on the patient, S. E., Table 3, who presented a typical clinical picture of pernicious anemia, cover a period of about five weeks, during which time he had, under observation, a spontaneous blood remission. The case offered opportunity to study the relation of the oxygen absorption to the percentage of the reticulated cells

under varying conditions in the same individual. Prior to the remission and after it had ceased, when the reticulated cells were not increased, there was no oxygen absorption. During the remission, however, as noted, there was an increased absorption of oxygen, which was coincident with the appearance of increased numbers of reticulated cells.

Table 4 gives the results of observations on blood samples from patients with anemia in which the percentage of reticulated cells was increased as indicated. The relationship between the percentage of the total oxygen absorbed and the percentage of the reticulated cells in the blood is apparent.

CONCLUSIONS

1. Normal mature human erythrocytes have no oxygen consumption measurable by present methods.

2. Where it is measurably increased in the blood of individuals with anemia, the oxygen consumption has no relation to the severity of the anemia and no constant relation to histologic abnormalities in the erythrocytes other than increases in the number of reticulated cells.

3. Blood which contains abnormal numbers of reticulated erythrocytes has an oxygen consumption proportional to the percentage of reticulated cells present.

4. The data afford evidence that the two phenomena go hand in hand. Both are due to the presence of abnormal numbers of youthful cells, and both are probably rather accurate indicators of functional variations in the bone-marrow and of the amount of blood regeneration.

THE PHYSIOLOGY AND EXPERIMENTAL TREATMENT OF POISONING WITH THE LETHAL WAR GASES *

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The gases employed in the recent war may be divided into four great groups, as follows:

1. Asphyxiant or suffocating gases. For example, chlorin, phosgene (COCl_2), diphosgene and chlorpicrin (CCl_3NO_2).
2. Tear gases or lachrymators. For example, xylyl and benzyl bromid.
3. Sneezing gases or sternutators. For example, diphenylchlorarsine.
4. Blistering gases or vesicants. For example, yperite or mustard gas ($\text{C}_2\text{H}_4\text{Cl}_2\text{S}$).

This division of gases is, however, only a rough classification, inasmuch as a gas may fall into more than one of the groups quoted. Thus a gas may have at least two different warfare uses, it may be both a lachrymator and an asphyxiant, or, again, it may possess suffocating properties in addition to a blistering action. The classification given above carries with it the conception that the placing of a gas in one or another group is on the basis of the most important effect elicited by a given gas.

MILITARY USE OF GASES

From the viewpoint of the military purpose for which gases are employed they may be divided into two large groups: (a) Lethal gases, and (b) neutralizing gases. Under the term of lethal gases are included all those gases used in warfare which are employed for the object of killing the enemy. The principal substances comprising this group are chlorin, phosgene (carbonyl chlorid) and chlorpicrin (nitrochloroform). On the other hand, extensive use was made of a large variety of gases the main purpose being not to kill the enemy, but to make him work under difficulties; in other words, to neutralize his military efficiency. Hence this group of substances received the name

* Read before the Harvey Society at the Academy of Medicine, New York City, March 15, 1919.

of neutralizing gases and included the lachrymators, the sneezing gases and the vesicants.

In general, the neutralizing gases produce effects on the human organism of a nature which cause discomfort rather than serious injury. On the other hand, many of these substances, if in sufficient concentration, are quite capable of inducing grave effects, or may even be the direct cause of death. For example, mustard gas was used primarily for its vesicant action, producing blisters which in certain cases might involve the entire skin and cause death in this manner; or a sufficient quantity of gas could be inspired so as seriously to injure the respiratory tract in such a way that the whole mucous membrane of the upper respiratory passages would peel off as a cast. Portions of this cast might get into the bronchi or bronchioles acting as a mechanical plug and interfere with respiration, causing death by asphyxia.

In general, the sneezing gases and the lachrymators induced effects, such as relatively slight irritation and congestion, which called for no special investigation to alleviate or to combat any detrimental influence. The treatment indicated in such cases was obvious. To a great extent the same may be said of the vesicant gases where the primary effect requiring treatment was the blister or the burn. In this instance a serious sequel to the gassing is dependent almost entirely on the evil effects of secondary infection. In the treatment of mustard gas effects the prevention of infection was the object aimed at, and it was attained by a variety of means, all of which were designed to keep the wound as aseptic as possible.

While these statements are true in general for these three groups of gases—the sneezing gases, the lachrymators and the vesicants—they are capable of producing additional effects if inspired in sufficient quantities. On the other hand, such effects were not especially prominent in producing casualties in the field, hence the exact character of these additional influences has not been extensively investigated.

THE LETHAL GASES

Of special importance in warfare have been the lethal gases. This group contains such substances as chlorin, phosgene and chlorpicrin. Other substances are also included in this group, but from a practical standpoint the gases named are the most important. Chlorin was the first gas employed, phosgene followed and then chlorpicrin appeared. These three substances are unlike in that chlorin and phosgene are gases, whereas chlorpicrin is a liquid. Chlorin and phosgene, especially when mixed, may be used in the form of a cloud, the first method of gas warfare. The perfection of the gas shell, however, increased

the number of substances that could be employed and greatly augmented the efficiency of gas as a means of warfare, inasmuch as the substance could be distributed in the area desired without dependence on the conditions of the wind or the dangers of the gas being blown back.

These three gases are alike in that each contains chlorin as an essential part of the molecule, and one might assume at first glance that the physiologic effects produced by phosgene and chlorpicrin are due to the action of the free chlorin or the hydrochloric acid formed as a result of the hydrolysis or other decomposition of the gases. This is an interesting hypothesis, but from the pathologists' findings it can hardly be true, inasmuch as the lesions produced in the three cases are quite distinct and specific.

The three gases are lachrymators as well as respiratory irritants. Chlorin is preeminently a respiratory irritant and is characterized by the extreme rapidity with which it produces its typical effects, namely, pulmonary edema and congestion. On the other hand, phosgene is less likely to cause immediate edema, but it is regarded as a more effective fighting weapon, as its use leads to a large number of casualties and deaths. The toxic action of phosgene is slower than that of chlorin, probably because to produce its effects it must undergo chemical change. This latent period in the action of phosgene has earned for it the name of having a delayed action. Chlorpicrin is not as rapid in action as chlorin, but produces its typical effects much sooner than phosgene. This gas is regarded as especially valuable from a military standpoint, since it penetrates masks more readily than either of the other two gases.

SYMPTOMS OF GAS POISONING

Chlorin.—Exposure of a dog to the gases elicits reactions which are quite characteristic for each gas. The general clinical symptoms induced by gassing with chlorin are, at first, general excitement, as indicated by restlessness, barking, urination and defecation. Irritation is distinctly evident as seen by the blinking of the eyes, sneezing, copious salivation, retching and vomiting. Later the animal shows labored respiration with frothing at the mouth. Food is refused, although a large quantity of water may be drunk. The respiratory distress increases until eventually death may occur from apparent asphyxiation. On the other hand, if the concentration of the gas is not lethal, the animal may present an emaciated appearance and be distressed greatly for several days. Ultimate recovery ensues with return to apparently normal conditions.

Phosgene.—Phosgene acts chiefly as a respiratory irritant, but it is also a lachrymator. Very small doses, scattered in the air, cause coughing, watering of the eyes, and intense dyspnea. It differs from chlorin in that in these small concentrations its influence is limited mainly to the terminal air cells of the lungs. This effect leads to edema of the lungs and consequent cyanosis, which may terminate in death. The first symptoms are dizziness and cyanosis on exertion. It usually takes several hours for the serious symptoms to develop, and in the interval there is no sign of danger.

At high concentrations there is slight lachrymation and uneasiness. The pupil becomes clouded, but the animal exhibits no violent symptoms. Subsequently there may develop a hard cough, respiration becomes more and more difficult, usually there is a rattling in the throat and death follows within the first twenty-four hours after exposure. The heart action grows weaker as death approaches but persists after all attempts at breathing have ceased.

Chlorpicrin.—Exposure to chlorpicrin causes coughing, nausea and vomiting, and in large quantity may cause unconsciousness. Secondary effects are bronchitis, shortness of breath, a weak, irregular heart and gastritis. It may also cause acute nephritis. Liquid chlorpicrin has a corrosive action on the skin, and scratches and abrasions exposed to chlorpicrin fumes invariably become septic. Abscess formation may result.

A comparison of the three gases shows quite plainly that chlorin has a very strong irritating action, the animal becoming excited and being in evident distress. With chlorpicrin the character of the reactions produced is very similar to those of chlorin poisoning, except that the symptoms are less pronounced. Phosgene, on the other hand, appears to cause the animal no immediate distress. Instead of becoming unduly excited the dog lies quietly in the chamber, and even when the symptoms appear hyperexcitability is not present. It would seem that a certain degree of peripheral anesthesia is present, handling the animal failing to act as a stimulus to muscular activity — struggling — so characteristic with chlorin and chlorpicrin dogs.

PATHOLOGY OF GAS POISONING*

Chlorin.—From the pathologic aspect chlorin produces injury to the organism by causing immediate death of the epithelium lining the upper respiratory tract. Areas of focal necrosis in the lung itself are attributed to the direct action of chlorin on parts of the lung not protected by bronchiolar spasm. The destruction of the epithelium of

*Taken from the reports of Dr. M. C. Winternitz.

the trachea and bronchi removes the normal protective mechanism of the upper respiratory tract and allows pathogenic bacteria from the mouth to find their way into the injured bronchioles within a very short period after the epithelium has been destroyed. This bacterial infection results in a pneumonia—lobar, lobular or necrotizing—the type depending on the organism concerned. The pneumonia is associated in all cases with an infection lesion of the bronchi. The infection tends to persist in animals surviving the acute period, resulting in a chronic bronchitis, organizing or obliterative bronchiolitis with scarring of the lung. Such lesions are demonstrable in dogs dying or killed as late as six months after gassing. The irritating action of chlorin results in a bronchiolar spasm, which, interrupting the normal inflow and outflow of air, causes an acute emphysema or atelectasis, most marked in animals dying in the acute stage.

Edema of the lungs, trachea and bronchi is the most striking feature of acute death from chlorin gassing. It is probably brought about by the direct action of the gas which so damages the bronchi and alveoli as to render the adjacent capillary wall permeable. The coagulation of the plasma as it passes out through the alveolar wall leads to the deposition of fibrin in this situation which must seriously interfere with the inflow of blood through the lung, thus putting a strain on the right side of the heart.

Phosgene.—With phosgene gassing the lesions seen at necropsy vary according to the length of time the animal survives after exposure to the gas. At first, a severe pulmonary edema is associated with extreme congestion which reaches a maximum after the first twenty-four to thirty-six hours, and disappears gradually in animals surviving ten days or longer. The edema is associated with an inflammatory exudation of fibrin and leukocytes, which is most marked in and around the finer bronchioles and which spreads through the lung tissue to a variable extent. A typical lobular or pseudolobar pneumonia is the result. The pneumonia is frequently complicated by a necrotization of the wall of the bronchus, which may involve the adjacent alveoli to form abscesses. On the other hand, the inflammatory process may be combated successfully, but in an attempt at healing foci of organizing pneumonia and obliterative bronchiolitis result. They constitute chronic foci of infection, as shown by bacteriologic studies.

The character of the phosgene lesion is explained by the localization of the action of the gas on the air tubes. The epithelium of the trachea and larger bronchi is not damaged, while that of the smaller bronchi and bronchioles is seriously injured, the more distal portion suffering most. In addition to the changes in the mucosa, the bronchi also show

pathologic contractions and distortions which result in the more or less complete obliteration of the lumen. These, in turn, lead to mechanical disturbances in the air sacs, resulting in a chronic condition of atelectasis or emphysema.

Chlorpicrin.—Chlorpicrin injures the epithelium of the entire respiratory tract, but all portions of the tract are not equally affected. The trachea and largest bronchi, though irritated, suffer only transient injury. The medium size and small bronchi are the most affected. There is a uniform and widespread damage of the alveolar walls which, however, is not severe enough to lead to necrosis. The alveoli are apparently nowhere protected by constriction of the bronchi.

The overwhelming edema of the lungs rapidly follows exposure to the lethal concentration of the gas. In extreme cases practically every alveolus is filled with fluid. In addition to the fluid in the lung itself there is also marked edema of the mediastinal tissues and pleura which is even more striking than in phosgene and chlorin gassing. The edema fluid contains fibrin and a great deal of fibrin is found in the alveolar walls. Partial or complete occlusion of the smaller bronchi by inflammatory exudate or masses of necrotic cells leads to focal emphysema or atelectasis, but this is not such a striking feature at necropsy as in the case of death from some of the other respiratory irritant gases, for example, phosgene. Infection of the lungs with the development of a widespread bronchitis and bronchopneumonia is seen in a large percentage of those animals which do not die in the first few hours after gassing. Abscess formation, pleurisy, fibrinous or purulent, and organizing pneumonia are common complications. In recovered animals there is a regeneration of the epithelium of the bronchi and alveoli and organization of the necrotic bronchiolar wall with scar formation. Focal atelectatic emphysematous patches remain as prominent gross evidence of the gas injury.

A comparative study of the pathology of chlorpicrin, chlorin and phosgene shows that chlorpicrin in its action on the respiratory tract occupies a position somewhere between chlorin and phosgene. It damages the trachea and larger bronchi less than chlorin, but more than phosgene. In its action on the bronchioles and alveoli it resembles phosgene very closely, but in several other respects the lesions are more like those of chlorin. The gross and microscopic differences in the effects of the three gases on dogs are sufficiently clear cut to enable an experienced observer to determine by necropsy which gas has been used.

INTERPRETATION OF GAS POISONING

In the time allotted it would be impossible to describe in detail the character of the various types of work carried through in our investigation on the war gases. It will suffice to say that under carefully controlled conditions the influence of the lethal gases on the organism of the dog has been studied both intensively and extensively. In this investigation several thousand animals were employed. As a result of this work it may be stated that pulmonary edema is the prominent feature of the effects induced by these gases. In addition to pulmonary edema, gassing has a definite influence on the respiration, heart beat, temperature, the concentration of the blood, the water content of the lungs and other tissues, the chlorid content of the blood and tissues with resulting changes in chlorid excretion by way of the kidney, the number of the red and white cells of the blood, and the respiratory function of the blood leading to dyspnea and partial asphyxia. Acidosis is present at times, and there is a distinct influence on protein metabolism. Some of these effects are, of course, dependent on the development of pulmonary edema, but others are not so readily explained in this way. It should be stated that so far as can be determined by experimental methods the lethal gases act specifically on the respiratory tract which action results in edema. Little or none of the gas is absorbed. Hence, whatever influence is exerted on the organism by these gases must be explained by an interpretation of the effects induced in the respiratory tract.

The effects of gassing, as enumerated above, are so various that an attempt at correlation or the assignment of cause and effect seems at first glance well nigh impossible. Further study of the problem, however, brings to light one significant feature which stands out clear and distinct from all the other effects induced by exposure to gas. This is the well defined curve of changes in blood concentration. On the basis of alterations in blood concentration quite definite stages in gas poisoning may be outlined. These stages stand out most clearly with phosgene, and therefore the picture presented by this gas will be considered first.

STAGES IN PHOSGENE POISONING

First Stage.—In the first few hours (5 to 8) after phosgene poisoning there is a notable decrease in the concentration of the blood. The decrease occurs rapidly and then the blood gradually tends to assume the normal concentration. In this period there may be significant dilatation of the heart (observed by Eyster). Accompanying the decreased

concentration of the blood there is a sharp drop in the chlorids of the blood and a marked increase in the chlorids and water content of the lungs. The chlorids of the urine increase immediately after gassing, reaching a maximum between the third and seventh hours, then decreasing. The heart beat is distinctly slowed at first with a tendency to regain the normal or be somewhat above the normal before this period is over. The immediate effect on the respiration is a distinct increase in the rate. During this period the temperature shows a marked increase, attaining a maximum coincident with the termination of this period. Oxygen capacity of the blood, the number of erythrocytes and hemoglobin follow a curve parallel with that of the changes in the blood throughout all stages of phosgene poisoning. The oxygen content of both arterial and venous blood decreases significantly. The saturation of hemoglobin with oxygen decreases somewhat. In general, the decrease is more marked in the venous than in the arterial blood. In the first period of phosgene poisoning an influence on protein metabolism is not noticeable.

Second Stage.—The period of blood dilution is followed by an interval during which the blood rapidly becomes concentrated to a point far above the normal value and remains near this level for several hours. In this stage the heart may be markedly decreased in size (Eyster). During the period of increased blood concentration the chlorids of the blood show a tendency to regain the normal. The water and chlorid content of the lungs reach a maximum and then gradually fall. The heart beat and respiration are both markedly accelerated. In animals that are in a serious condition, although the rate of respiration is markedly increasing, there is a decrease in depth so that rapid, shallow breathing exists. The temperature steadily decreases to a degree or more below normal. If the animal dies in this stage, the temperature may fall steadily up to the time of death. Most of the fatalities occur in this stage. The oxygen content of arterial blood remains fairly stationary at a nearly normal value, whereas that of venous blood falls rapidly to a very low level. The saturation of hemoglobin with oxygen decreases rapidly in both arterial and venous blood but the fall is greater in venous blood. There is no evidence of an influence on protein metabolism.

Third Stage.—After the period of increased concentration the blood gradually becomes more dilute until it is slightly under the normal value, which is eventually gained, and the animal recovers. The chlorids of the blood gradually tend to regain the normal level. The chlorid and water content of the lungs follows a similar course. In animals reaching this stage, the heart beat and respiration rise to a maximum

and then gradually attain the normal. The temperature rises to normal or above in those animals that eventually recover. In those animals that die during this period the heart beat and respiration rise but the temperature steadily falls. The oxygen content of arterial and venous blood tends to regain the normal. Chlorid excretion by the kidney is markedly decreased but later is much augmented. Coincident with the increased chlorid excretion is a noticeable increase in the protein metabolism.

Summary.—The interpretation which may be placed on the different stages of phosgene poisoning is as follows: In the first stage there is marked dilution of the blood. There are at least two ways in which this dilution may be explained. In the first place it may mean an increased blood volume, the excess fluid finding its way into the blood from the tissues in response to the strong irritation stimulus exerted by the gas on the respiratory tract. Second, a diluted blood would result if the red cells were removed in part and deposited in some organ or tissue. In the present investigation no studies were made to determine actual changes in blood volume. Reports by Eyster and Meek, however, who have made such estimations, tend to the conclusion that in the stage of phosgene poisoning under discussion blood volume is not increased, and they account for the dilution of the blood on the hypothesis that red cells are stored in the lungs, at least temporarily. Whichever explanation is correct, it is certain that during this first stage two features may be quite prominent, namely, edema of the lungs and dilatation of the heart. Edema can be explained very readily on the hypothesis of increased blood volume and it is also possible that such a condition might lead to a dilated heart. On the other hand, the deposition of corpuscles in the lungs, by causing an obstruction in the circulation, would lead to a dilated heart. The relatively large transport of fluid to the lungs during this period is, however, not so easily explained by this hypothesis. Whichever hypothesis is accepted, edema of the lungs prevails and there may be a dilated right heart.

In the second period edema has reached its maximum development and here also blood concentration is at its height. The latter state is undoubtedly induced by the withdrawal of fluid which finds its way into the lungs. During the interval of blood concentration the blood volume is definitely decreased and the heart may be noticeably diminished in size (Eyster). This would presumably result in a decreased efficiency of this organ and lead to an inadequate circulation. Later when the blood resumes its normal degree of concentration, normal heart action is reestablished.

The development of edema induces a mobilization of chlorids in the lungs at the expense of the chlorids of the blood, the lowered

chlorid content of which may be explained in part by loss of chlorids through the kidneys, since at this period the output of chlorids in the urine is appreciably augmented. Later, during the second stage, the chlorids of the lungs reach a maximum, the blood content is not called on and therefore an approximately normal blood chlorid content may be found which is maintained thereafter. This chlorid retention by the lungs coincides with the fact that on the second day of phosgene poisoning the urinary excretion of chlorids is usually below normal. The period of readjustment now follows, during which edema subsides in the lungs, and presumably both fluid and chlorids are demobilized by the lungs and find their way into the blood. The excess of chlorids over the normal in the blood is eliminated through the kidneys, which would account for the large output on the third day after gassing.

The changes in oxygen capacity, erythrocytes and hemoglobin follow the curve of alterations in blood concentration throughout the entire course of phosgene poisoning which might well be anticipated. Oxygen content of arterial blood in general shows relatively unimportant changes, whereas that of venous blood progressively diminishes throughout the first and second periods of phosgene poisoning. This may be explained in the first period by the fact of diluted blood and in the second period is undoubtedly caused by the longer contact of the blood with the tissues induced by an inefficient circulation.

The respiratory changes are correlated with the impaired respiratory functions of the blood, such as lowered oxygen content and incomplete saturation of the hemoglobin with oxygen.

In the first stage decreased heart rate may be explained best, perhaps, on the hypothesis of nervous inhibition. The later rapid pulse is directly induced by the viscous character of the blood which causes oxygen want. Although specific data are lacking, it appears quite evident that there is a distinct fall of blood pressure. One may assume a direct relationship between the heart's efficiency and temperature. Thus, in the first part of the first stage the heart action is slow, there is inefficient circulation, and the temperature falls. Later the greatly accelerated pulse is accompanied by a rise in temperature far above the normal. From this it would appear possible that the heart has temporarily overcompensated resulting in an efficiency of the circulation above the normal.

Now follows the stage of concentration of the blood. This concentrated blood is, without doubt, more difficult to circulate through the body and if the heart is only doing its normal work there will be, as a result of the thickened blood, a circulation of less than normal efficiency and such a condition apparently results in a falling temperature.

In case the heart responds with a much higher rate during the period of concentration, so that even with the thickened blood it appears that a circulation of close to normal efficiency is being maintained, it will be found that the temperature is also well maintained.

In the animals which are less seriously affected and in which only a slight edema of the lungs develops, with a consequent slight loss of fluid from the blood, it will be found that the temperature is well maintained, provided the heart rate is normal. However, even in such cases, the continuous even though slight loss of fluid from the blood will eventually result in a concentration of the blood which will bring the circulation below normal efficiency, even with a high pulse rate, and the temperature will drop slowly until at about the twenty-fourth hour it is about 1 C. below the normal. On the other hand, in the animals which are seriously affected, the blood concentrates very rapidly. The heart, even though the rate is maintained far above normal, is nevertheless not able apparently to maintain a circulation of normal efficiency, the temperature drops very rapidly and the animal dies within less than twenty-four hours after gassing.

In brief, then, it seems plausible that the temperature is directly related to the efficiency of the circulation and this in turn is determined, in part at least, by the concentration of the blood and the pulse rate.

This view seems to be further strengthened by the results obtained from a study of animals gassed with chlorin and chlorpicrin. In both of these cases there is, in general, a state of concentration of the blood beginning immediately after gassing. Only in rare instances does dilution of the blood occur and then it is only for a short time. From the first, then, in animals poisoned with these last named gases, there obtains a condition in which the blood is above normal in concentration and in correspondence with this the temperature remains below normal and the more seriously the animal is affected and the greater the concentration of the blood, the greater will be the fall in temperature.

Phosgene poisoning has been considered in detail since it is unique in showing among its effects the initial stage of dilution of the blood. At times chlorpicrin presents a similar stage but this interval is never so pronounced either in degree or length as obtains in phosgene poisoning. Usually a preliminary dilution period is lacking. It is this period that undoubtedly gives to phosgene the distinction of possessing a so-called "delayed action." Chlorin gas rarely, if ever, causes a period of blood dilution. In general, if one should consider the changes in blood concentration outlined for phosgene, minus the initial dilution period, the remaining curve would represent fairly accurately the alterations occurring in the blood in both chlorin and chlorpicrin poisoning. This would, of course, entail differences in time relationships, but

under the conditions noted the changes in blood concentration of chlorin and chlorpicrin would be accompanied by the same general type of effects which is obtained with phosgene. Under these circumstances it appears superfluous to recite further the correlation of the effects of chlorin and chlorpicrin poisoning.

CAUSE OF DEATH IN GAS POISONING

It is generally assumed that the cause of death in gas poisoning is due directly to edema of the lungs aided, of course, by the accompanying congestion. It has been said that death is caused by an individual literally drowning in the water of his lungs. The quantity of water may reach as high as a liter or more, and such a conception as the cause of death seems quite obvious. On the other hand, one may well ponder whether death is usually induced in this way or whether there may be some other cause to which one may point with more certainty. The most obvious condition, other than edema, which could lead to death is the concentration of the blood. Of course, it is evident that edema and blood concentration are closely associated. Edema is assuredly the cause for blood concentration, and thus indirectly at least brings about death, but it would appear that blood concentration is much more likely to produce death than is the presence of fluid in the lungs. Two possibilities are therefore to be considered.

Death by edema could be caused by the prevention of an adequate oxygen supply in the pulmonary blood. On the other hand, through extensive experiments of Winternitz* it is quite possible to introduce large quantities of fluid directly into the lungs of normal dogs without causing death, the fluid being absorbed with surprising rapidity. It must be conceded, however, that the conditions obtaining in the lungs of a normal dog and in those of a gassed animal are quite different, for in the experiments cited simple salt solution was introduced, whereas in the edematous lung the fluid more nearly represents blood plasma. Such a fluid would have a much greater tendency to inhibit adequate oxygen exchange than would a simple salt solution. The adherents of the idea that edema is the cause of death must ascribe death to asphyxiation. There is little doubt that well developed edema does interfere with oxygen exchange of the pulmonary blood, but usually the efficiency of the arterial blood as an oxygen carrier is surprisingly high. It would seem a simple matter to put the question to the test experimentally. Thus, it might be assumed that if edema is the cause of death, this operating by producing asphyxia, administration of oxygen should save the animal provided the oxygen could be

* Unpublished.

absorbed. Such experiments have been carried through in this investigation and the results have demonstrated that though the oxygen in the arterial blood may be raised and maintained within the higher normal limits, death intervenes as usual. Then again, some animals seem to die with much less edema than others and the different gases also possess different degrees of ability in provoking edema. If edema is the cause of death it is difficult to explain why some animals with an apparent excessive quantity of fluid in the lungs should survive. Death is caused by something more than simple inability of the blood to absorb oxygen, by something more than a physical obstacle in the lungs.

It seems quite logical to assume that blood concentration is immediately responsible for death. Blood concentration means a failing circulation, an inefficient oxygen carrier, oxygen starvation of the tissues, fall of temperature and finally suspension of vital activities. The whole aim of treatment in gas poisoning has been to prevent blood concentration or else restore it to a level more nearly normal. When this is accomplished the animal survives in spite of the fact that the lungs may be very edematous. It may be stated, then, that in the presence of edema and a concentrated blood, entrance of oxygen into the circulation does not prevent death. On the other hand, restoration of blood to a more normal concentration enables an animal to survive even though an extensive edema exists. Administration of oxygen under the last named conditions undoubtedly makes recovery easier.

Therefore, while it is accepted that indirectly the edema of gas poisoning results in death, the immediate cause of death must be assigned to blood concentration.

TREATMENT OF PHOSGENE POISONING

From the foregoing considerations it is quite apparent that changes in blood concentration constitute the most important and significant action of phosgene on the animal organism. It is therefore quite logical that in any endeavor toward alleviation of the effects of phosgene poisoning efforts should be directed toward the restoration of the blood to a concentration more nearly approximating the normal.

It must also be evident that for the successful accomplishment of such a purpose there should be some criterion, or criteria, which shall indicate time of treatment and if possible type of treatment. Such criteria are to be found in changes in temperature and in hemoglobin estimations. Both are very simple procedures and best results are obtained when they are employed in conjunction. There are conditions, however, especially in the field where hemoglobin estimations may be impracticable. Under these circumstances treatment may be applied

successfully in accordance with the temperature changes alone. should be stated that hemoglobin determination is selected inasmuch as it may be substituted for the more arduous total solid estimation. Changes in hemoglobin and total solids in gassed dogs follow similar if not exactly parallel courses and hemoglobin estimation is a much more sensitive test for changes in blood concentration than is total solid determination.

In accord with these principles an outline of the treatment evolved in this investigation is as follows:

Treatment of First Stage.—Approximately one hour after gassing, blood is drawn from a vein to the extent of one per cent. of the body weight. Bleeding at any time up to four hours after gassing is beneficial, but the best results are obtained when the withdrawal of blood is practiced about an hour after gassing.

Treatment of Second Stage.—In the first stage blood concentration may exhibit one of two features after bleeding. (a) The blood becomes markedly dilute and slowly returns to normal concentration. (b) There is no significant dilution of the blood. The latter is an exceptional condition. The time of further treatment will therefore depend on which of these two conditions obtains. When the blood becomes markedly dilute and then slowly returns to the normal, infusion of 0.97 per cent. sodium chlorid solution, equal in amount to the blood withdrawn, should be practiced when the blood concentration regains the normal level. This usually takes from eight to ten hours. On the other hand, when even after bleeding the concentration of the blood is not definitely decreased, infusion of salt solution should be delayed until there is a clear indication that the blood is becoming concentrated. This usually occurs from six to eight hours after gassing. In any case the infusion should not be delayed beyond the point where the blood has reached a concentration of more than 25 per cent. above normal.

After the infusion of the salt solution the concentration of the blood is followed at one hour intervals by determination of hemoglobin in order to ascertain whether subsequent salt infusion is indicated. In general, after the first infusion the blood may begin to concentrate again within one hour and when this concentration continues it may be desirable to infuse subsequently, but judgment must be exercised in order to strike a proper mean between insufficient and excessive infusion. Insufficient infusion leaves the blood concentrated. Excessive infusion augments edema. So long as the concentration of the blood remains constant, infusion is unnecessary, and when the concentration diminishes the individual is on the road to recovery.

Treatment of Third Stage.—Usually rest and warmth are all that are necessary in this stage, but if the blood should become greatly diluted again and remain so a further bleeding may be necessary. This condition, however, occurs rarely.

The principles of treatment are, therefore, very simple—venesection when the blood is diluting and infusion of salt solution during the initial period of blood concentration. Venesection tends to diminish the degree and extent of dilution. Infusion of salt solution tends to keep the blood concentration at a level where it is possible to maintain an approximately efficient circulation; in other words, blood concentration is kept at a level where an animal may survive. Infusion actually accomplishes this, and when properly practiced does not augment pulmonary edema.

The treatment as given must be considered as a mere outline of the principles followed rather than as a recital of the detailed procedure. Experience with the method soon showed that intensive treatment in the first stage of phosgene poisoning, that is, in the period of dilution, will, in the majority of cases, prevent extreme concentration of the blood characteristic of the second stage. In other words, the second stage is very greatly modified by proper treatment of the first stage. During the first stage water should not be given.

Proper treatment of the first stage consists in venesection to the extent of 0.5 per cent. body weight as soon after gassing as practicable. The temperature and hemoglobin are then followed at one-half hour intervals. So long as the temperature remains normal and blood concentration does not diminish, further treatment is not indicated. When, however, the temperature rises rapidly and a fall in blood concentration occurs (the two changes take place simultaneously) a second venesection of 0.5 per cent. body weight is practiced. This procedure may be repeated a second time, that is, until blood to the extent of 1.5 per cent. of the body weight has been withdrawn. The large majority of cases need no further treatment and practically every animal survives.

If in spite of intensive treatment in the first stage the blood becomes markedly concentrated and a marked fall in temperature takes place, the condition of the animal must be considered as very serious, and if left untreated the animal will surely die. At this point, of course, infusion of salt solution is indicated.

The essential feature in the stage of blood concentration is to diminish if possible the degree of concentration, and we have found by experience that it matters little how this is attained. Thus this purpose may be accomplished by infusion of salt solution, by oral administration of water or even by intraperitoneal injection of salt solution. Probably one half the animals in a serious condition in this stage of

blood concentration may be saved by following either procedure. The fact that fluid by mouth or peritoneal cavity acts with about the same efficiency as direct infusion into the circulation increases the practicality of the method when applied to man under field conditions where in many instances infusion into a vein would be out of the question.

The efficiency of the method of treatment may be realized from the following figures. When dogs are gassed at a concentration of eighty to ninety parts phosgene per million of air for one-half hour and given no treatment, 21 per cent. recover. Under the same conditions, treatment as outlined enables 63 per cent. of animals to recover. Presenting it differently, treatment increases the recoveries three-fold.

With respect to the treatment of chlorin and chlorpicrin poisoning the principles enunciated for phosgene hold true. While the principles are the same there is a difference in the time of application, for in general in chlorin and chlorpicrin poisoning the initial stage of dilution is lacking. With phosgene early bleeding and delayed infusion are advocated, with chlorin and chlorpicrin early bleeding and early infusion are imperative. Moreover, in chlorin poisoning there is evidence of a significant acidosis, hence, administration of sodium bicarbonate by mouth is advocated, in addition to the treatment outlined for phosgene.

When dogs are gassed with chlorin at a concentration of 800 to 900 parts per million of air for one-half hour and given no treatment, 9 per cent. of the animals recover. Under the same conditions with treatment as outlined, 30 per cent. of dogs recover.

When dogs are gassed with chlorpicrin at a concentration of 110 to 130 parts per million of air for one-half hour and given no treatment, 43 per cent. of animals recover. With treatment, 80 per cent. recover.

Various other types of infusion fluids such as other salt solutions, dextrose solutions, acacia solutions, etc., have been tested in an endeavor to obtain a blood diluent which would remain in the circulation for a considerable period. An extended experience has shown that none of these solutions answered our purpose so well as simple isotonic sodium chlorid solution.

The results of the treatment as given justify the conclusion that the factor in gas poisoning exerting the greatest detrimental influence is the alteration in blood concentration, and further, that if blood concentration can be controlled a gassed individual has very fair chances of recovery from the effects of the gas.

OXYGEN IN THE TREATMENT OF GAS POISONING

Lack of oxygen in certain stages of gas poisoning plays a significant rôle. There is little or no evidence of an inadequate supply of oxygen

in the arterial blood during the first part, if not the whole of the first period. When, however, blood concentration becomes marked, insufficient oxygen in the arterial blood is quite apparent. In this investigation changes in blood concentration have been assumed as the responsible factors leading to the condition of anoxemia. According to this view the viscosity of the concentrated blood leads to impaired circulation in the tissue capillaries, thus accounting for the extremely low oxygen content of the venous blood, which is so characteristic of gas poisoning.

The question naturally arises, "Will administration of oxygen eliminate anoxemia?" Again, if anoxemia is alleviated will this allow the individual to survive the effects of phosgene poisoning? From clinical experience there seems to be conflicting evidence as to the value of oxygen in the treatment of gas poisoning. On the whole, however, it would appear that the consensus of opinion indicates that oxygen administration is decidedly beneficial in the circumstances under discussion. On the other hand, from an experimental viewpoint, oxygen as the only treatment of gas poisoning appears to have very little value, inasmuch as just as many gassed animals die when continuously kept in an atmosphere of 50 per cent. oxygen as without oxygen treatment. Though this conclusion is inevitable from the data, it must be conceded that oxygen administration seems to relieve the animal. It rests more quietly, respiration is less difficult and obvious cyanosis disappears or is absent.

An analysis of the situation reveals the reason for the failure of oxygen to change the death rate in phosgene poisoning. Oxygen administration to lethally gassed dogs may improve markedly or even restore to normal the oxygen content of arterial blood, without, however, significantly increasing the content of the venous blood. In those instances where venous oxygen content is maintained within approximately normal limits recovery follows. The same thing may occur, and to the same extent, without oxygen treatment. It is therefore quite evident that though arterial blood contains sufficient oxygen the tissues are undergoing oxygen starvation. Oxygen treatment alone does not strike at the fundamental difficulty, namely, oxygen starvation induced by an inadequate circulation. The concentrated blood is responsible for the inefficient circulation, and if the condition of the gassed individual is to be improved, measures must be taken to restore the blood to a concentration at which life is possible. It has been found that when the blood is treated in this way by the method outlined, sufficient oxygen may be provided for tissue respiration without oxygen administration. It is a significant fact, however, that bleeding and infusion followed by oxygen administration results in the restoration

of both arterial and venous blood to approximately normal conditions with respect to oxygen content. It would appear from these facts that bleeding plus infusion so changes the physical character of the blood as to render possible a more complete oxygenation of the tissues.

From another viewpoint the value of oxygen in treatment is indicated. Exposure to phosgene diminishes appreciably the oxygen consumption. Breathing oxygen under these circumstances increases oxygen consumption. Bleeding slightly increases oxygen consumption although it is still below normal. It is thus apparent that venesection increases somewhat the ability of the animal to obtain oxygen. Breathing oxygen after venesection still further raises oxygen consumption. Infusion raises the oxygen consumption to a still higher level. Oxygen administration after infusion brings the oxygen consumption back to the normal level and may indeed carry it above. This should be considered in connection with the percentage saturation of arterial and venous blood. As has been pointed out above, the administration of oxygen after infusion results practically in complete saturation of the arterial blood as well. The oxygen consumption is equal to or greater than normal; while the arterial blood is almost completely saturated and the venous percentage saturation indicates that the tissues are getting an ample supply of oxygen.

The conclusion is therefore warranted that the method of treatment involving venesection, infusion and oxygen administration is definitely indicated for the reestablishment of normal conditions in the respiratory functions of the blood in an animal gassed with phosgene. Under these circumstances recovery is made possible.

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